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# EXTENSIVE ATHEROMA AND DILATATION OF THE PULMONARY ARTERIES, WITHOUT MARKED VALVULAR LESIONS, AS A NOT VERY RARE CAUSE OF FATAL CARDIAC DISEASE IN BENGAL

By LEONARD ROGERS

With Plates 1–4

As long ago as 1901, while performing a post mortem at the Medical College, Calcutta, I met with a remarkable condition of extensive dilatation and atheroma of the pulmonary arteries, accompanied by extreme hypertrophy and dilatation of the right ventricle and auricle, without any valvular disease whatever, although the case had been diagnosed during life as one of mitral regurgitation. While indexing and examining the old post-mortem records I came across similar cases in the time of my predecessors as pathologists, and subsequently several others have occurred, so that this disease is by no means the extreme rarity in Bengal that it would appear to be in temperate climates, judging from the paucity of references to it in the medical literature I have been able to consult in Calcutta. It therefore appears to be advisable to delay no longer in placing these cases on record, especially as they do not appear to have been previously recognized during life, although they present fairly characteristic histories and symptoms, doubtless on account of the supposed almost entire exemption of the pulmonary vessels from extensive disease, except of a congenital nature.

Thus, I have not been able to find any reference to this disease in Allbutt's *System of Medicine*, while Osler only mentions one case as having been recorded by Romberg. Broadbent, in the fourth edition of his work on *Heart Diseases and Aneurism of the Aorta*, does not mention atheroma of the pulmonary artery. A. E. Sansom, in his work on diagnosis of diseases of the heart and in his article in Vol. IV of *Twentieth Century Medicine*, states that chronic endarteritis and atheroma is much rarer in the pulmonary artery than in the aorta, the former vessel being less likely than any other large artery to show atheroma, according to the tables of Rokitansky, Lobstein and Huchard, although when it does occur the lesions are similar to those of the aorta, and lead to dilatation of the pulmonary artery. He refers to the following cases: one of destruction of the pulmonary valves by atheroma and dilatation of the pulmonary artery, together with a congenital communication between the two ventricles, in a girl of 20 the subject of syphilis, recorded by Bruen; Romberg's



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case of extensive sclerosis throughout the pulmonary artery and its branches, with consecutive hypertrophy of the right ventricle, without any congenital lesion. Tommasi Crudeli has recorded general dilatation of the pulmonary artery with small sacular aneurysms just above the valve, while James Barr is also quoted by Sansom as having observed that the majority of cases of pulmonary atheroma are associated with obstructive disease of the lungs or mitral valve diseases, especially mitral stenosis.

The first of the cases recorded below resembles Bruen's in that both the pulmonary artery and valve were affected, but in the remaining nine the disease was essentially one of the pulmonary arteries, without inflammatory or degenerative lesions of any of the cardiac valves.

### Pulmonary Atheroma with Deformity of the Pulmonary Valves.

*Case I.* The earliest example I have been able to find is a remarkable specimen of disease of the pulmonary artery and valves in the Calcutta Medical College Museum, fully described by the late Dr. J. F. P. McCannell, I.M.S., in the museum catalogue and in the post-mortem register of 1877. As I have not been able to trace any record of it in the medical journals of that time or reference to it in recent literature, it appears to be well worthy of a place here.

*Clinical History.* The patient was a Hindu male, aged 38, and a blacksmith by occupation. He was admitted to hospital on April 6, 1877, and died on the 15th of the same month. There was both a history (and scars) of previous syphilis, and also of rheumatism and intemperance. He had suffered from pain in the chest for two years, but palpitation and general anasarca had appeared only during the last two months. On admission there was general anasarca and ascites. The cardiac dullness was much increased, but the heart sounds were feeble and distant, and the impulse imperceptible. A soft systolic bruit was heard over the apex, which was only conducted a short distance to the left. No murmurs were heard over the aorta or pulmonary artery. The pulse was small and feeble, and he complained of giddiness and faintness on the slightest exertion. The dyspnoea and anasarca diminished during the first week in hospital, but the former increased on the 14th, and he died rather suddenly the following morning after a few gasping respirations.

*Post Mortem.* The pericardial sac was about the size of an adult head, and contained nearly two pints of clear yellow fluid. The right cavities were greatly distended with post-mortem clot. The right auricle was greatly dilated, and the coronary sinus admitted the tip of the forefinger. The tricuspid orifice admitted five fingers, while the venae cavae were much dilated. The right ventricle was greatly dilated and its wall dissected out. Its endocardium was greatly thickened, being leathery, rough and corrugated. The pulmonary orifice was very wide and quite incompetent, while the valves were greatly deformed. The right valve was thin and stretched. The central valve had almost disappeared, forming a tightly stretched, semi-transparent band across the pulmonary artery, while the wall of the vessel immediately above it was aneurysmally

dilated to the size of half a walnut. The left valve lay at a lower level than the other two, its left half being thin and stretched, and its right thickened and flattened so as to form a prominent transverse ridge across the pulmonary orifice. The pulmonary artery was extensively diseased; its coat was as thick as the aorta and leathery, its inner surface being rough, opaque and irregularly thickened. The vessel was formed into an hour-glass-like dilatation by a constriction two inches above the pulmonary orifice. The lower dilatation had the form of a huge bulbar expansion measuring five and a half inches at its greatest diameter, while the upper one measured five inches across, its inner surface being greatly corrugated and wrinkled. The foramen ovale was closed and the ductus arteriosus obliterated. The left cavities of the heart were small in comparison with those of the right, their muscular walls being of about normal thickness. The mitral and aortic valves, and the lining membrane of the aorta, showed nothing abnormal in their structure, the aortic orifice being also normal. On dissection it was found that the pulmonary artery, instead of dividing into right and left branches, curved to the right without giving off the left pulmonary vessel, and then divided into five or six large branches, from one of the lower of which a vessel passed to the left lung between the pericardium and the descending aorta. The other organs were healthy except for enlargement of the liver and congestion of the abdominal viscera.

In this case the very large effusion into the pericardium (for which aspiration was not practised) obscured the physical signs of the valvular disease. The right ventricle showed great dilatation, with but little hypertrophy, owing to the extreme deformity of the pulmonary valve leading to a rapid heart failure. The evidence of syphilis in this case was quite clear. The extraordinary dilatation of the coronary sinus was doubtless associated with the extreme degree of hydropericardium, and was also found by me in Case X (before I was aware it had been observed in the above case), having been specially looked for on account of the frequency of marked hydropericardium in the present series.

## Nine Cases of Extensive Atheroma and Dilatation of the Pulmonary Arteries with great Hypertrophy and Dilatation of the Right Cavities.

*Case II. Clinical History.* A Hindu female, aged 55, admitted on November 17, 1894, under Dr. Bomford (now Director-General of the Indian Medical Service) from the out-patients, with a history of having suffered from palpitation for two or three years, and cough, with shortness of breath, for two weeks. She was said to have suffered from an attack of rheumatism twelve years before (true rheumatic fever is, however, exceedingly rare in Calcutta), after which she had good health up to about three years ago, when she began to get palpitation, at first slight, but slowly increasing and accompanied by difficulty of breathing. About fifteen days previously great dyspnoea came on at night, which was still present.

On admission the apex beat was very marked in the epigastrium, where a loud systolic bruit was heard, not conducted to the axilla. The pulmonary

second sound was not accentuated. The pulse was soft and feeble. Râles and rhonchi were heard all over the lungs, and expiration was prolonged and wheezing. The liver was enlarged and tender on pressure, but the spleen was normal, and there was no fever. During the two weeks she was in hospital the dyspnoea increased, although the cough became less, and she was very sleepy. On the 25th the apex beat was noted at the left border of the lower part of the sternum, with a loud systolic murmur over it, very faintly conducted towards the axilla, and not heard in the pulmonary or aortic areas. Death took place suddenly. The diagnosis was mitral regurgitation (tricuspid regurgitation ?).

*Post mortem* performed, December 1, 1894, by the late Major J. F. Evans, I.M.S. (who subsequently died of plague contracted while investigating the post-mortem pathology of that disease). There was some clear fluid in both pleural cavities, and 6 oz. in the pericardium. The heart was markedly enlarged, large milk-spots being present over the front of the right ventricle and pulmonary artery, the latter being enormously dilated and filled with decolorized post-mortem clot. The corpora Arantii of the pulmonary valves were markedly enlarged, and there was a line of old vegetations (? thickening) at the margins of the cusps. Numerous minute atheromatous patches were found at the commencement of the pulmonary artery, which extended into the enormously dilated branches entering each lung. Some of the patches were calcified, but others appeared to be breaking down. The right side of the heart was very much hypertrophied and dilated. The triscuspid orifice was considerably wider than normal, but the valves were quite healthy. The left ventricle was quite healthy, while there was only very slight thickening of the margin of the anterior cusp of the mitral valve. The aortic valve was healthy, and there was only a slight atheromatous condition at the commencement of the aorta.

The lungs were slightly emphysematous at the anterior border only, and rather blackish-brown in colour. The liver was much engorged with blood and showed a fairly well-marked nutmeg appearance. The spleen was intensely congested, and contained a calcareous nodule the size of a pea, probably the remains of an old gumma. The kidneys were congested, and showed a slightly granular surface, but the capsule stripped easily. The gastro-intestinal tract also showed congestion of the mucous membrane. The cause of death was described as due to atheroma and dilatation of the pulmonary arteries, leading to hypertrophy followed by dilatation of the right ventricle and tricuspid regurgitation.

*Case III.* The *post mortem* was made on October 4, 1896, by Major Evans, on the body of a Hindu female, aged 23, who had been in the women's hospital three days for delivery of a child. (Clinical notes not available.) There was slight oedema of the ankles, and 1 oz. of fluid in the pericardium. The heart weighed $10\frac{1}{2}$ oz. The wall of the right ventricle was much hypertrophied, and the tricuspid opening was normal. The pulmonary artery was dilated, being much larger than the aorta, and measured 3 inches in circumference just above the pulmonary valve, against $1\frac{3}{4}$ inches just above the aortic valve. On slitting up the pulmonary arteries into the lungs, several large atheromatous patches were found. The left ventricle was dilated and its wall thin, but the mitral and aortic valves were normal.

The right lung was congested, as were the liver and spleen. The kidneys only showed post-mortem changes. The brain showed calcareous patches in the dura mater, but was otherwise healthy. The genital organs were healthy except for a slight laceration of the cervix of the physiologically enlarged uterus.

In this instance the patient appeared to have died of failure of the left ventricle during labour, the atheroma and dilatation of the pulmonary artery found post mortem having been largely compensated for by hypertrophy of the right ventricle. The occurrence of marked pulmonary atheroma in a woman of only twenty-three is noteworthy.

*Case IV.* The *post mortem* was made on September 5, 1897, by Major Evans, on the body of a Hindu male, aged 32, who died on the day of his admission to hospital, without a diagnosis having been made. The body was poorly nourished. The pleural cavities were healthy, but the pericardium contained 5 oz. of clear fluid without any signs of pericarditis. The heart was considerably enlarged, and the right cavities distended with blood. The empty organ weighed 12½ oz. The right ventricle was much hypertrophied and dilated, but the tricuspid orifice barely admitted three fingers. The pulmonary artery was competent to the water test, but its lumen was very much dilated. Its walls showed extensive atheroma, which extended into its tributaries in the lungs up to subdivisions smaller than a crow-quill. The left ventricle was dilated, but its walls were not thickened. The mitral orifice admitted two fingers, while the aortic valve was competent to the water test. The first part of the aorta only presented some fibrous thickening of the intima.

The right lung weighed 19 oz., and showed some wedge-shaped pale consolidated areas, and a haemorrhage as large as a walnut, directly connected with a small branch of the pulmonary artery. The left lung was free from consolidation and weighed only 9½ oz. The liver was congested and showed some fatty and cirrhotic changes. The spleen weighed 8½ oz. and was healthy. The kidneys only showed congestion, while the gastro-intestinal tract was healthy. The cause of death was returned as atheroma of the pulmonary artery and dilatation and hypertrophy of the right ventricle.

This is a typical case of the disease terminating in dilatation of the previously hypertrophied right ventricle. The recent haemorrhage in the right lung and the consolidated areas, apparently due to older ones, are of special interest. The final cardiac failure appears to have been rather sudden.

*Case V.* A Hindu female, aged 12, married, admitted into Dr. Harris's ward on August 15, 1898, from the out-patients for mitral disease.

*History.* Six months before she got fever, which has recurred every three or four days since then. During this time she has suffered from dyspnoea and palpitation on slight exertion. Some five months ago she first noticed oedema, beginning in the face and extending to the arms and legs, while it had now become general.

*Condition on Admission.* She complained of dyspnoea and palpitation, was anaemic and always drowsy. The face, eyelids, legs and feet showed marked oedema, while there was much fluid in the abdomen. The pulse was 87, and very small and soft. The apex beat was very diffuse, most marked

inside the nipple. The cardiac dullness stretched from the second left cartilage and the right border of sternum to one inch inside left mid-axillary line. A very marked presystolic bruit was heard all over the cardiac dullness from below the second rib, being most marked 1½ inches inside the nipple and below it in the fourth to the sixth spaces. The superficial veins of the chest and abdomen were prominent. The respirations were 40 per minute and shallow, with great dyspnoea. The lungs were resonant all over and normal on auscultation. The liver and spleen were not enlarged. The urine was high coloured, sp. gr. 1016; a trace of albumen was present.

*Progress.* The dyspnoea continued to be very distressing, preventing her sleeping, although she was always drowsy. Constant very severe headache was also present, possibly of syphilitic origin. The oedema increased and the feet became cold. Signs of oedema at the bases of the lungs appeared, and on September 3rd 128 oz. of clear fluid were removed from the abdominal cavity by tapping, which relieved the dyspnoea to some extent. The fluid rapidly reaccumulated, and 96 oz. more were removed on September 24th, and 196 oz. on October 12th, with only very temporary good effect. The dyspnoea and oedema continued to increase and death took place on November 7th. But little change in the sounds of the heart were noted while she was in hospital, except that a marked pulmonary systolic murmur and reduplication of the second sound were once noted. The presence of the presystolic bruit was recorded up to two days before death. The temperature was usually subnormal and only once rose as high as 99·4° F.

*Diagnosis.* Mitral constriction?

*Post mortem,* made on November 8, 1898, by Major Evans. There was very marked general anasarca of the subcutaneous tissues, and marks of paracentesis of the abdominal cavity having been performed. The left pleura contained 3 oz. of clear fluid and the right one 18 oz., while the pericardium contained 15 oz. and the abdomen over 150 oz. The blood appeared to be watery. The distended pericardium measured seven inches in its greatest diameter and occupied the greater part of the thoracic cavity, the lungs being partially collapsed. The right cavities of the heart were distended with blood clot. The right ventricle was much hypertrophied, measuring a quarter of an inch at its thickest part, while the cavity was considerably enlarged. The tricuspid valve admitted three fingers. The pulmonary valves were normal and competent to the water test. The wall of the pulmonary artery was undoubtedly thickened and the vessel dilated, while its intima displayed areas of fatty degeneration, but there were no atheromatous patches. The ductus arteriosus was obliterated. The left ventricle was healthy, measured half an inch at its thickest part, and contained a little blood clot. The mitral valve was normal and the orifice admitted the tips of two fingers. The aortic valves appeared to be competent, and the intima of the thoracic aorta was fairly normal.

The lungs were small and showed little areas of splenization. (There was rusty sputum during life.) The bronchial glands were enlarged and displayed old caseous disease. The liver was pigmented and distinctly nutmeg in character, and its surface rough from adhesions to the diaphragm. The spleen was healthy, and the kidneys only showed congestion and some haemorrhages in the mucous membrane of the pelvis. The gastro-intestinal mucous membrane was congested and oedematous, and there was a tubercular ulcer in the lowest part

of the ileum, while the mesenteric glands were enlarged and showed a few caseous points on section. The brain showed a considerable degree of sub-arachnoid oedema, but was normal on section. Death was returned as having been due to arteritis of the pulmonary artery with dilatation and hypertrophy of the right ventricle. The old tubercular disease is interesting but not uncommon in post mortems in Calcutta.

The occurrence of extensive disease of the pulmonary arteries at the early age of twelve years is very remarkable in this case, while such a chronic arteritis as was here found might well have originated the atheromatous condition seen in the other cases at a later age. In India acquired syphilis, unfortunately, cannot be excluded by her youthful age.

*Case VI.* The *post mortem* was made on January 28, 1901, on the body of a Hindu female, aged 36, who had been in hospital for five days for abdominal tumour and mitral regurgitation. (Clinical notes not available.) There was much oedema of the subcutaneous tissues all over the body, and marks of leech-bites in the right hypochondrium and of paracentesis of the abdomen. There were 18 oz. of fluid in the abdomen and 1 oz. in the pericardium. The pericardium was uncovered by the lungs and greatly distended, reaching from three inches to the right of the median line to touch the left wall of the chest. Its parietal layer and the base of the heart showed numerous ecchymoses, while there was a large milk-spot over the right ventricle. The right cavities and venae cavae were enormously distended, 45 oz. of dark fluid blood escaping on opening the great vessels. The heart weighed 16¼ oz. The right auricle was greatly dilated and its walls thinned. The right ventricle was very dilated and its walls hypertrophied. The tricuspid valve just admitted four fingers. The pulmonary valve was healthy and competent to the water test, but the pulmonary artery was very wide, and 1½ inches above the valves numerous small opaque atheromatous patches were seen. The left ventricle was dilated and its walls thin. The mitral orifice admitted three fingers, and the anterior cusp showed small atheromatous patches. The aortic valve was competent, while just above it were some very faint atheromatous patches. The endocardium of the left ventricle was opaque.

The lungs were very small and tough, and of a dark blackish-red colour, being deficient in air. They weighed 11 oz. and 12½ oz. respectively. The liver was firm and tough, and its surface slightly rough. The spleen was reddish black in colour and fibrous. The kidneys were small and firm, capsule slightly adherent, but left a smooth surface; their weights were 3¾ oz. and 4 oz. The gastro-intestinal mucous membrane was congested. The cause of death was returned as dilatation of heart with mitral and tricuspid regurgitation. In this case there was some dilatation of the left ventricle, but the marked hypertrophy and dilatation of the right ventricle appeared to be associated with the extensive atheroma and dilatation of the pulmonary arteries.

*Case VII.* A Hindu female, aged 35, admitted under Dr. Bomford on October 3, 1902, from the out-patients for mitral regurgitation and ascites.

*History.* She had had small-pox eighteen months ago. Five months previously she noticed swelling of her face and legs, and a week later intermittent fever came on and lasted for two months, and after it left her the abdomen

became swollen, and palpitation and exhaustion appeared on slight exertion. Nausea and sickness next came on with epigastric pain.

*Condition on Admission.* A hard mass was felt in the position of the pylorus. Anaemia and general anasarca, including the face, was present. The left heart was hypertrophied and dilated, extending to one inch inside the anterior axillary line, the impulse being in the sixth space, where a systolic murmur was heard. The pulse was small and irregular. The lungs were healthy and the spleen not enlarged. The urine showed a trace of albumen; its sp. gr. was 1015.

*Clinical Diagnosis.* Mitral regurgitation.

The *post mortem* was made on November 2, 1901, by the writer. There was extensive general anasarca. The abdominal cavity contained 32 oz. of clear fluid, the pleural cavities 6 oz., and the pericardium 4 oz. The heart weighed 13½ oz., being greatly enlarged. The right auricle was distended by 5 oz. of post-mortem clot; its cavity was much dilated, and its walls hypertrophied. The tricuspid valve admitted three fingers, the cusps being slightly thickened. The right ventricle was distended with post-mortem clot. It was greatly dilated and also extremely hypertrophied, its wall measuring half an inch in thickness, being thicker than the left ventricle, while its apex extended distinctly beyond that of the left ventricle, thus forming the apex of the organ. The left auricle was normal. The mitral orifice admitted the tips of three fingers, and the cusps were normal except for slight thickening of the edge. The left ventricle was empty and normal. The aortic valves were normal, but the commencement of the great vessel was markedly atheromatous and dilated. The pulmonary valves were competent to the water test, but the pulmonary arteries were extremely atheromatous and so greatly dilated that the index-finger could be readily passed deeply into the lungs in several directions through the main subdivisions of the vessels. On cutting through the lungs the greatly dilated, thickened, and atheromatous pulmonary arteries were so striking a feature as to be mistaken at first sight for a condition of bronchiectasis.

The lungs appeared to be healthy with the exception of the pulmonary arteries. The liver extended one inch below the costal margin, and presented a nutmeg condition. The spleen was rough on the surface from adhesions and showed fibrosis. The kidneys and intestines were healthy.

It was this very striking case which first directed my attention to the disease. The healthy normal state of the left side of the heart contrasted greatly with the enormous hypertrophy and dilatation of the right cavities, while the extent of the atheroma of the pulmonary arteries, and still more the enormous dilatation they had undergone, constituted a most remarkable picture quite unlike anything I had previously seen in an experience of many hundred post mortems in England and India.

*Case VIII.* The *post mortem* was made on March 23, 1903, by Lieut.-Col. Drury, I.M.S., on the body of a Mohammedan male, aged 40, who had been in hospital for twelve days, his disease being diagnosed as mitral regurgitation. (Clinical notes not available.) There was marked oedema of the subcutaneous tissues, and 160 oz. of ascitic fluid were found in the abdomen, a few ounces in each pleura, and 13 oz. in the pericardium, which was not covered by the lungs and extended from 2½ inches to the right of the middle line to the left chest wall, and

upwards as high as the sternal notch. The whole of the anterior surface of the heart was formed of the right ventricle and the pulmonary artery, the latter being dilated and its intra-pericardial portion firmly adherent to the parietal pericardium and the aorta. On opening the large vessels 22 oz. of blood flowed into the pericardium. The right auricle was distended and its walls thin. The right ventricle showed several small milk-spots on its surface, while on section it was found to be much hypertrophied, and the musculi papillares much enlarged. The tricuspid orifice admitted four fingers, the valves being normal. The pulmonary valve was healthy and competent to the water test, but the vessel measured four inches across at the level of the valves. The walls of the pulmonary artery were very thin, and commencing about 1½ inches above the valve were numerous plaques of yellowish-white atheromatous thickening, which extended a considerable distance into the lung. The left ventricle also showed some dilatation, and its walls were thick. The mitral orifice admitted two fingers, being slightly narrowed, and its edges slightly thickened. The aortic valves were competent to the water test, and showed slight thickening at their attachment. The aorta showed slight atheromatous thickening, which extended throughout the thoracic and abdominal portions of the vessel.

The lungs were of a dark reddish-brown colour, and rather deficient in air, while the left apex showed a haemorrhagic infarction, over which the pleura was puckered, showing it to be of some standing. The liver was firmly adherent to the diaphragm, and showed a dense gummatous patch extending into its substance, and general mottling and fibrosis. The spleen was congested and fibrous. The kidneys were much congested; the capsule stripped easily and left a slightly granular surface. They weighed 4½ oz. and 5½ oz. The gastro-intestinal mucous membrane was congested, especially that of the large bowel. The brain showed excess of arachnoid fluid, and was moist-looking. The cause of death was returned as being due to dilatation and atheroma of the pulmonary artery. This is another characteristic case of an advanced type.

*Case IX.* A Hindu male, aged 20, an agriculturist, admitted under Dr. Harris on January 6, 1908, from the out-patients for mitral disease. No history of rheumatism, venereal disease, or alcoholism was obtained. The family history was good.

*Present Illness* began 1½ months ago with slight evening intermittent fever for a few days, with slight cough. After the fever ceased, breathlessness and palpitation on exertion with dry cough remained, and after about eleven days he noticed swelling of his legs, which spread all over his body, subsiding partially at times.

*Condition on Admission.* He was slightly anaemic. The face was puffy, and general anasarca was present all over the body, together with some ascites. The sleep was disturbed by dyspnoea and discomfort on lying on his left side. There was visible pulsation in the veins of the neck, but the cardiac impulse was not seen. A diffused impulse was felt in the normal position, and a faint thrill in the third left space. The cardiac dullness extended from the third left cartilage and the right edge of the sternum to one inch outside the nipple line. A loud systolic murmur was heard over the mitral region, conducted towards the axilla. The second pulmonary sound was accentuated at the base and reduplicated at the apex. The pulse was weak, but regular, and 90 per minute.

The lungs were normal. The liver was moderately enlarged, but the spleen could not be felt. The urine was scanty and high coloured.

*Clinical Diagnosis.* Mitral disease.

The *post mortem* was made on January 20, 1908, by the writer. The body was fairly well nourished and showed extensive anasarca extending up over the chest wall. The peritoneal cavity contained 80 oz. of dropsical fluid, the pleural cavities 10 oz. and 12 oz., and the pericardium 3 oz. The heart weighed 8½ oz. The apex of the right ventricle extended slightly beyond that of the left. The right cavities were greatly distended with blood, the right auricle being much dilated and the ventricle both dilated and hypertrophied, its wall measuring one-third of an inch in thickness, being almost as thick as the left ventricle. The tricuspid valve admitted four fingers and the valve showed slight thickening. The pulmonary valve was healthy, but the artery was dilated and measured 5½ centimetres across at its root, against 4½ in the aorta. The wall of the pulmonary artery showed extensive raised yellow patches of atheromatous thickening, which extended far into its tributaries in the lungs, although they were less numerous than in some of the former cases. The left cavities of the heart were healthy. The mitral valve admitted the tips of three fingers and its cusps were healthy. The aortic valve was healthy and competent to the water test, and the commencement of the great vessels was also normal, except for one small patch of atheroma in the descending part of the arch.

The lungs were partially collapsed and congested, but there was no consolidation. The liver was congested and in a nutmeg condition, and firmer than normal. The spleen was dark and firm. The kidneys only showed slight congestion. The stomach was healthy and the intestines showed some congestion. Death was due to hypertrophy and dilatation of the right heart secondary to atheroma and dilatation of the pulmonary arteries.

In this case the cardiac changes were somewhat less marked than usual, the heart having given out in a comparatively early stage of the disease.

## A Case of Pulmonary Atheroma correctly diagnosed during life.

*Case X.* On my reporting the result of the post mortem on Case IX to Lieut.-Col. Harris, I.M.S. (to whom I am greatly indebted for permission to use the clinical notes of Cases V, IX, and X), he kindly asked me to see with him a very obscure cardiac case then in his wards, the history of which is as follows:—

*Clinical History.* A Hindu male, aged 23, a cultivator, was first admitted to hospital under Dr. Harris, from the out-patient room, on February 28, 1907, for mitral disease. He had previously been subject to attacks of dyspepsia and constipation. Nine months before admission these recurred together with slight occasional fever in the evenings, and two months later he first noticed occasional palpitation and slight dyspnoea after any exertion, such as a walk or hard work. At the same time he observed that his abdomen was swelling, and then oedema appeared in his feet, and later in his legs, hands and face, and all over his body, which increased up to his coming to hospital. On admission he had general anasarca all over his body, including his face, while the abdominal cavity contained free fluid. His face was markedly cyanosed and he suffered much

from dyspnoea. The pulse was very slow, only 54 beats a minute, but was regular and of low tension. The apex beat was but slightly to the left of the normal position, while epigastric pulsation was well marked. A thrill could be felt in the pulmonary area in the third left space, which extended towards the apex. There was a systolic murmur at the apex, which was conducted slightly towards the axilla. The pulmonary second sound was almost replaced by a marked regurgitant murmur, while a pulmonary systolic murmur was also heard at times, although not constantly present. The liver was felt to be slightly enlarged, but not hard or tender; the lungs were healthy, but the urine was very scanty.

The *Progress* of the patient under treatment with cardiac tonics and diuretics was remarkable. The excretion of urine rapidly increased, and the dropsy decreased, until on March 11th it had disappeared even from his legs, while the tension of his pulse improved. On April 17th he was discharged cured, all dropsy, dyspnoea and cyanosis having completely disappeared. The disease was returned as congenital disease of the pulmonary artery.

*Relapse and Readmission.* On January 14, 1908, he was readmitted to hospital from the out-patients with a diagnosis of mitral disease. He stated that against medical advice he had resumed his work as a cultivator after leaving hospital, and about six weeks later symptoms of giddiness and oedema reappeared, and he was treated by quacks in his native village without relief. The oedema increased and he became giddy on the slightest exertion, so he returned to hospital.

*Present Condition.* There was general oedema all over the body, including marked puffiness of the face, while the abdomen contained free fluid. He was markedly cyanosed and suffered from dyspnoea, worse at night. The apex beat was seen in the fifth space in the nipple line, while there was a well-marked diffuse impulse to the left of the sternum about the third space, in which situation a very distinct presystolic thrill could be felt, which was also present in a lesser degree at the apex. The cardiac dullness on admission extended upwards to the lower border of the second left costal cartilage and laterally from just to the right of the sternum to slightly beyond the nipple line. On auscultation in the aortic area both sounds were distinct and no murmurs heard. In the pulmonary area there was a loud double murmur, the diastolic one being most marked and best heard in the third left space. At the apex both a systolic and a diastolic murmur were heard, the former being conducted slightly towards the axilla, while the latter could be traced down to the apex from the pulmonary area. The pulse was slow and regular, but small, being totally unlike the pulse of aortic regurgitation. Dr. Harris had diagnosed the disease as pulmonary, but thought it was probably congenital stenosis on account of that being by far the commonest affection of the pulmonary valves. He also considered that there was, in addition, mitral disease on account of the double murmur at the apex.

At the time I first saw the patient I had just analysed the post mortem and clinical notes of the former cases, and at once recognized the very close similarity in the history and symptoms to those of the preceding cases. Further, the fact that in several of the earlier post mortems of this series the right ventricle had been so much hypertrophied that it formed both the whole of the anterior surface of the heart, and that its apex also extended

beyond that of the left ventricle, seemed to me to afford a simple explanation of most of the difficult points in the case, on the hypothesis that the disease was one of dilatation and atheroma of the pulmonary artery. Thus, if the apex beat was really that of the right ventricle, then the conduction of both the pulmonary diastolic murmur and of the presystolic thrill (the latter being due to the powerful action of a greatly hypertrophied right auricle) from the pulmonary area to the position of the apex beat at once became clear. The formation of the apex beat by the hypertrophied right ventricle would also account for the former cases having almost invariably been diagnosed as mitral disease, when that valve had been found quite healthy after death; for murmurs heard over the apex of the heart would naturally be referred to the left ventricle by any one who had no reason to suspect the altered relationship of the apices of the two sides of the heart to the chest wall. The regular slow small pulse, which was so inconsistent with either aortic or mitral regurgitation, became at once intelligible if the lesions were all on the right side of the heart. I therefore suggested that the disease was purely pulmonary regurgitation, most likely due to atheromatous disease of the pulmonary vessels, in view of the previous post-mortem evidence of the frequency of that condition in former cases presenting a similar history and symptoms to this one.

*Progress.* The dropsy and dyspnoea steadily increased in spite of all treatment, and towards the end the presystolic thrill disappeared and the pulmonary murmurs became less distinct, while the cardiac dullness increased, these changes being subsequently found to be due to hydropericardium; and he died in the early morning of February 28, 1908.

*Post Mortem.* I performed a post mortem six hours after death, being indebted for the opportunity for doing so to Lieut.-Col. C. P. Lukis, I.M.S., Principal of the Medical College, who had taken a great interest in the case. The whole of the subcutaneous tissues were very oedematous, and the abdominal cavity contained nearly two pints of fluid. The pleural cavities were obliterated by adhesions except at the extreme right base, where there was a small collection of clear fluid. The pericardium was greatly distended by 24 oz. of clear yellow fluid without any lymph deposits. It extended from one inch to the right of the sternum to the left mid-axillary line, where it was covered with a thin layer of compressed left lung, and upwards almost to the sternal notch. The whole of the anterior surface of the heart was formed by the right ventricle, while the apex of that cavity extended half an inch beyond that of the left ventricle, thus forming the apex of the heart, so that the left ventricle did not come into contact with the anterior thoracic wall. There was a large milk-spot over the front of the right ventricle, and another on its posterior aspect. The tricuspid orifice admitted the tips of four fingers, and the edges of the cusp showed slight thickening, but no sign of any inflammatory condition. The pulmonary valve was moderately incompetent to the water test, having doubtless been much more so during life when distended by the blood under high pressure. Its cusps were healthy except for the corpora Arantii being very large. The pulmonary artery was greatly dilated, measuring 4 inches in circumference at the level of the valves, almost twice as much as the measurement of the root of the aorta in a similar position (Plate 1). The first $1\frac{1}{2}$ inches showed very little atheroma, but patches were seen at the bifurcation of the main vessel. On opening up the pulmonary arteries into the lungs they were found to be greatly

dilated throughout those organs, and showed numerous yellow patches of atheroma down to the smallest vessels which could readily be slit up with a finely pointed scissors (Plate 2). The right auricle was very greatly dilated and hypertrophied, measuring 6 inches across after being laid open, while its walls showed very marked muscular bands, and measured in places as much as a quarter of an inch in thickness. The right ventricle was also greatly hypertrophied and dilated, the musculi papillares being very prominent, and its wall measured nearly half an inch in thickness, almost as much as that of the left ventricle (Plate 3). The left auricle was normal; the mitral valve was healthy and its orifice admitted the tips of three fingers. The left ventricle was normal, and the aortic valve competent to the water test, and its cusps were healthy. The root of the aorta showed a few small yellow patches of atheroma, and similar very slight affection was found at the origin of the great vessels from the arch and one small patch in the descending part of the arch, the rest of the vessel being quite healthy.

The right lung was rough on the surface from adhesions, crepitant throughout, but slightly oedematous. The left lung showed similar changes, but was small and somewhat firm from compression by the distended pericardium. The bronchial lymphatic glands were somewhat enlarged and pigmented. The liver was large and smooth on the surface, and on section showed a typical nutmeg appearance. The other organs were not examined, as permission had only been obtained to do a partial post mortem. Thus the diagnosis made during life was fully verified post mortem, the left side of the heart being quite healthy, while the enormous hypertrophy and dilatation of both the right auricle and ventricle were secondary to extensive atheroma and dilatation of the whole of the pulmonary arteries, and independent of any valvular lesions whatever. Another noteworthy feature was the great dilatation of the coronary veins, which at their entrance into the right auricle readily admitted the first joint of my little finger, while on opening them up they were found to be very much wider throughout than normal. This must have been due to back working of the high blood pressure in the extremely hypertrophied right auricle, and accounted for the excessive hydropericardium found post mortem.

### Microscopical Appearances.

Sections have been cut of the pulmonary arteries in four cases (including one of well-marked disease of the main trunk found in a patient who died of dysentery), and each showed typical atheromatous changes. The drawings in Plate 4 will serve to illustrate them, having been made from the vessels of Case X. Fig. 1 is from an atheromatous patch in one of the smaller distributing branches of the pulmonary artery deep in the lung, while Fig. 2 is from a larger patch near the bifurcation of the main trunk. The former shows an elongated thickening of the internal coat to the right, and a shorter, but deeper and abruptly rising, thickening to the left, which involves both the inner and the middle coats of the artery. Relatively to the size of the vessel these lesions are very marked, and as they were very widely distributed throughout the pulmonary arteries down to quite small tributaries, and were

accompanied by great dilatation of the vessels, the extreme hypertrophy and dilatation of the right cavities resulting from it can be readily understood. Fig. 2, from the main pulmonary trunk, shows advanced atheromatous changes. To the left is seen an irregular thickening of the intima, forming undulations on the inner surface, and these extended for a considerable distance beyond the portion there depicted. To the right is a more uniform and extensive thickening, with small-celled proliferation, while beneath this a badly staining degenerated layer is seen shading off into the middle coat, although the latter is not very extensively involved. The lesions, then, are quite typical of atheroma, and do not differ in any material point from similar changes in the systemic vessels. They are all the more remarkable as occurring practically exclusively in the pulmonary arteries, with little or no involvement of the aorta and other large vessels in this series of cases.

## Discussion of the Cases.

In considering the foregoing cases it will be well to deal first with the pathological changes recorded, and to point out the most constant features of the disease. In the first place the cause of death is clearly due to failure of the right ventricle, extreme dropsy, together with ascites, nutmeg liver and other signs of tricuspid regurgitation, being well marked. The frequency with which hydropericardium terminated the affection is another striking feature, which was present in varying degree in every case except the two in which cardiac failure ensued on labour very shortly after child-birth in a comparatively early stage of the disease. Thus, in four cases from 3 oz. to 6 oz. of fluid were found in the pericardium post mortem, in two more 13 oz. and 16 oz., and in Cases X and I no less than 24 oz. and 40 oz. respectively. In the last two instances extreme dilatation of the coronary veins and their opening into the right auricle was present, admitting the end of a finger in each instance, which was associated with great dilatation and hypertrophy of the cavity, leading to obstruction to the return of the venous blood from the cardiac veins.

Next, the extreme degree of hypertrophy and dilatation of the right ventricle is most noteworthy, and of the greatest clinical importance. Thus, in several of the cases the right ventricle was actually considerably larger than the left, and both constituted the whole of the anterior surface of the organ and also formed its apex, as shown in Plate 1. This character accounts for the disease having been almost invariably mistaken for some mitral affection clinically, for any murmurs generated in the right ventricle will be heard at the extreme apex of the heart, and will pretty certainly be attributed to defects of the mitral and aortic valves by any one who has no reason to suspect that the apex is formed solely by the right ventricle, and that the left cavity does not touch the chest wall. It is only when the altered relationship is found post mortem, together with an entire absence of disease of the valves of the left side of the

heart, that the true nature of the disease usually becomes clear. The small, and generally regular, pulse, of rather low tension, is an important point in excluding aortic disease and mitral regurgitation.

Another striking point is the absence of disease of the pulmonary valves themselves in all except Case I, in spite of the extensive atheroma of the pulmonary arteries. This feature appears to be associated with the fact that the first part of the main trunk of the vessel may be much less affected or almost entirely escape, while the distributing branches within the lungs are extensively involved, as in Case X. It is not improbable that in such cases the disease has not infrequently been overlooked hitherto. The cusps of the pulmonary valve may show some fibrous thickening, and also enlargement of the corpora Arantii, as in Fig. 1, due to the increased pressure, but they are very rarely affected by the arteritis or atheroma itself. Similarly the tricuspid valve may also show some slight fibrous thickening. Again, it was frequently noted that the pulmonary valves were competent to the water test in spite of the great dilatation of the vessel. I do not, however, think that this can be taken as excluding pulmonary regurgitation during life, for when the vessel is suddenly distended by the large volume of blood the hypertrophied and dilated right ventricle must eject, the orifice may be sufficiently stretched to allow of regurgitation, although water under no pressure may not readily flow back through the opening post mortem. In Case X there was clear clinical evidence of marked pulmonary regurgitation, although post mortem the pulmonary cusps were so wide as nearly to close the dilated orifice and only allowed a moderate amount of water to run through them.

The extensive dilatation of the whole of the pulmonary arteries, with or without actual regurgitation through the pulmonary orifice, must throw great stress on the right cavities of the heart. As the disease will usually be gradual in its onset, hypertrophy of the right ventricle and auricle first takes place, and commonly reaches such an extreme degree as to bring about the characteristic reversal of the normal relationships between the relative sizes of the two sides of the heart, so that the right ventricle becomes the larger of the two, and forms the apex of the organ. Sooner or later the right cavities become dilated and tricuspid regurgitation, with its attendant dropsy and nutmeg liver, ensue. Acute dilatation, without much hypertrophy, may occur under any sudden strain, as in the two women who died of this disease after child-birth.

The extensive haemorrhagic infarcts in the lungs in one case, together with consolidated patches due to older lesions of the same nature, indicate that the disease of the pulmonary vessels may be so great as to lead to the rupture of small branches under the excessive pressure produced by the hypertrophied right ventricle.

The incidence and predisposing causes of the disease are also of interest. The most remarkable feature here is the preponderance of the affection among females. Thus, in spite of the fact that three-fourths of the patients in the Medical College Hospital are males, yet five out of the ten cases occurred in

females, although ordinarily atheroma is much more common in males. The explanation appears to be that the essential cause of the affection is syphilis, which is appallingly common among natives of India, and especially in large towns like Calcutta, while the class of females who enter the open wards of the Medical College Hospital are all derived from the lower classes, among whom venereal disease is extremely common. The frequency of this cause also best accounts for pulmonary atheroma being so much more prevalent in India than it appears to be in European countries. Gummata were found post mortem in one case, while in another a calcareous patch was found in the spleen, probably the remains of an old gumma.

The comparatively young age of most of the patients for atheroma is also noteworthy, and in accordance with syphilis being the essential cause of the disease. Thus, the youngest patients were 12 (a married female), 20, 22, and 23 years of age, five were between 31 and 40, and one was 55. It is clear from these figures that the disease is not a degenerative one of old age, so that syphilis appears to be the only explanation of its causation. In the youngest patient the disease appears to have been rather of the nature of chronic arteritis, but in no case was there any evidence of an acute or malignant arteritis as the cause of the disease. It should be mentioned that fairly extensive systemic atheroma is not rarely met with in natives of India at a comparatively early age, such as about 30 years, while slighter degrees are quite common at that period of life. This tendency to early degeneration of the large vessels may partly account for the special incidence of the syphilitic virus on the pulmonary vessels in India, where both rheumatic fever and scarlatina are very rare, and the commonest cause of fatal cardiac disease is atheroma of the aortic valves: an important fact which alters the whole clinical aspect of heart cases in Calcutta.

The character and duration of the symptoms in several of the cases was also remarkable. In two cases there was a history of palpitation and dyspnoea on slight exertion for two and three years respectively before admission to hospital; in two for five months. In Case X these symptoms, together with oedema, had persisted for seven months; he recovered from an extremely dropsical condition under treatment by rest and cardiac tonics, and only returned to hospital seven months after his first discharge. In this case the compensatory hypertrophy was very marked (see Plates 1–4), so that the absence of actual valvular lesions in this disease affords hope of prolonged rest allowing compensatory changes in the heart to take place, which will allow of the circulation being maintained for a long time, if all hard work and strains are avoided.

The frequency of an extreme terminal hydropericardium, due to dilatation of the coronary veins of the heart, should be carefully borne in mind, for its onset is so insidious that it is nearly always overlooked, and paracentesis should afford great relief or at least prolong life.

## Summary.

1. Extensive atheroma of the whole of the pulmonary arteries, with no marked disease of the systemic vessels, and without any valvular affection, is a not very rare cause of fatal cardiac dropsy in Bengal.

2. It produces extreme hypertrophy and dilatation of the right cavities, which may be so great that the right ventricle forms both the apex and the whole of the anterior surface of the organ; and as a consequence clinically these cases have always been diagnosed as due to left-sided valvular disease, with the exception of one case recognized during life by the writer.

3. They occur nearly always between the ages of 20 and 40, and are almost certainly syphilitic in origin.

4. Palpitation, dyspnoea, and great dropsy due to tricuspid regurgitation are the principal symptoms, but they may be recovered from, for a time at least, under appropriate treatment. Death may occur in a fairly early stage from some severe strain, such as child-birth, but many of the fatalities result from a terminal hydropericardium of insidious onset, and accompanied by dilatation of the coronary veins of the heart.

## DESCRIPTION OF PLATES

PLATE 1 ($\times$ 1). Showing the dilated pulmonary artery, hypertrophy and dilatation of the right ventricle, which forms the apex of the heart, extending half an inch below that of the left ventricle. where, on the left, is seen a wall of normal thickness.

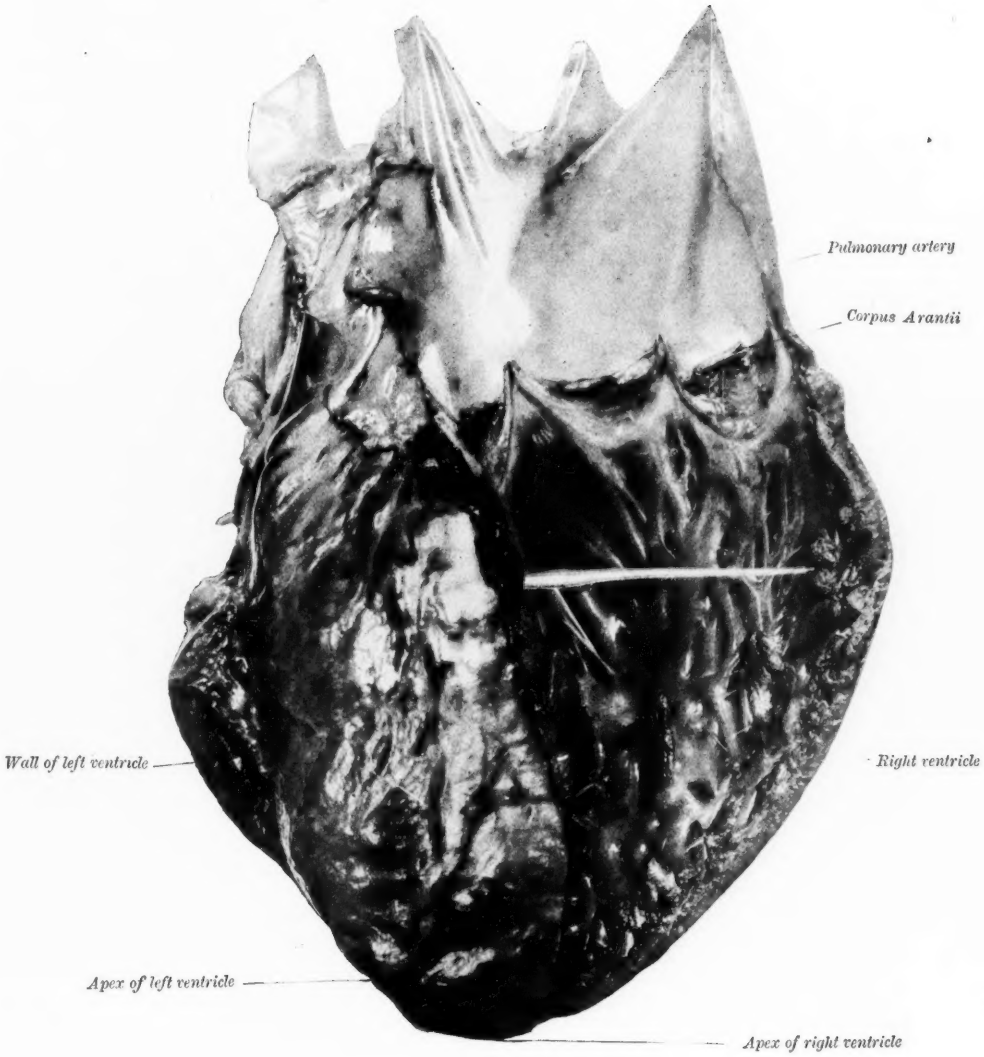
PLATE 2 (slightly reduced). The right lung, with the pulmonary artery and some of its branches, is laid open and shows the dilatation and atheroma of its vessels and numerous small patches of atheroma.

PLATE 3. The right auricle and ventricle, showing the extreme hypertrophy and dilatation of both cavities.

PLATE 4. Atheroma of the pulmonary arteries.

FIG. 1. Section of a small branch of the pulmonary artery in the middle of the lung.

FIG. 2. Section of the main pulmonary artery near the bifurcation.


Pulmonary artery
Corpus Arantii
Wall of left ventricle
Right ventricle
Apex of left ventricle
Apex of right ventricle

Coronary sinus

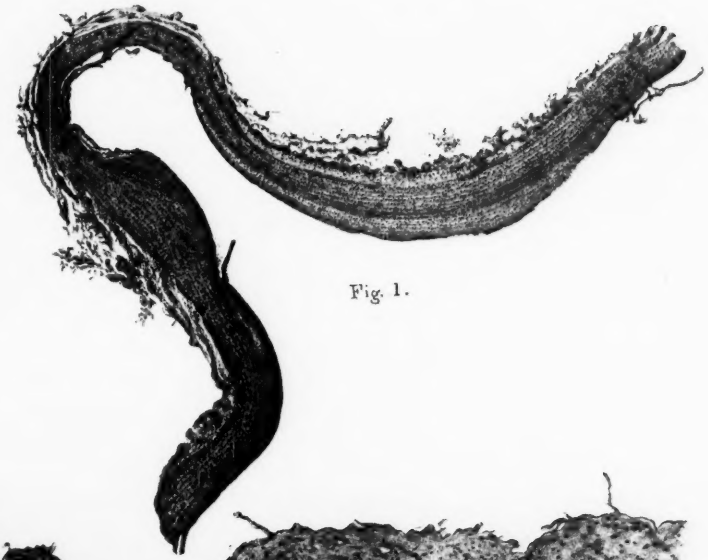


Fig. 1.

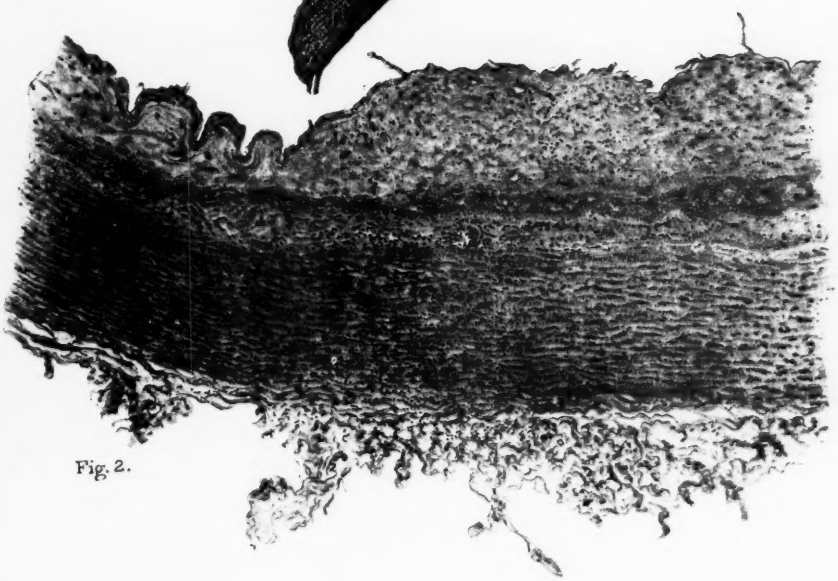


Fig. 2.

# COMPLETE HEART-BLOCK

By A. M. GOSSAGE

THE subject of Heart-Block and its association with the Stokes-Adams syndrome has attracted a great deal of attention during the last few years, and a large number of cases have been reported. Researches in Anatomy and Physiology, together with clinical records, have cleared up much of its obscurity, but there are still several problems connected with the subject which require elucidation. It may be taken as proved, that under ordinary circumstances the stimulus which causes the ventricle to contract is conducted from the auricles along a peculiar strand of muscle, the band of His. The conductivity of this strand varies, as may be shown by the length of the interval between the contractions of the auricles and the ventricles. In cases of depressed conductivity this interval is longer than the normal, or, in other words, the stimulus takes a longer time to pass along the connecting strand of muscle. With further depression ventricular beats are dropped out, so that there may be 3 beats of the auricles to 2 of the ventricles, or 2 to 1, or 3 to 1, and so on. It is also possible for the conductivity in this band to be completely abolished, so that there is no connexion between auricles and ventricles. This does not necessarily stop the working of the heart, but auricles and ventricles may continue beating quite independently of one another.

Both this condition and cases of marked depression of conductivity without complete block are associated with peculiar attacks in which the ventricles cease to beat for prolonged periods. Following this cessation of the ventricular beat the patient suffers from giddiness, loss of consciousness, general convulsions or apoplectiform coma according to the length of time that the ventricles are not working, the cause of the symptoms being evidently the cerebral anaemia. No satisfactory explanation has been offered for the occurrence of these attacks in cases of interference with the conductivity between auricles and ventricles. It has been suggested that nervous impulses by way of the vagus may further depress conductivity, so as to produce for a short time a complete block, during which the ventricle, not being accustomed to act by itself, remains stationary. That vagal influences do depress conductivity is well known both from animal experiments and from some clinical experiences with man. This explanation, however, cannot apply to cases of complete block, like the one here recorded, in which occur attacks exactly similar to those where the block is incomplete. It is possible, however, for the vagus to produce a standstill by depressing contractility as in the classical experiment of tetanizing the frog's vagus.

Sometimes after one of these Stokes-Adams attacks the heart, on beginning to beat again, starts with a small beat followed by beats that are successively larger until the normal size is regained just as in the physiological experiment. This is especially noticeable in Webster's curves (*Glasgow Hosp. Reports*, 1901), and it is very suggestive that, in this case at least, the attack was due to vagus influence on contractility. In most cases, however, as in Figs. 2 and 3, the first beat after an attack is the same size as the ordinary beats between the attacks. Erlanger too (*Journ. of Experiment. Med.* VII, No. 6, and VIII. No. 1) has pointed out that with complete destruction of the bundle of His in dogs the vagus has practically no influence on the ventricles. One must conclude, therefore, that this influence of the vagus on contractility is not the cause of all the attacks in cases of the Stokes-Adams syndrome, though it may account for some of them. It is, besides, difficult to understand why cases with disease of the bundle of His should be more liable to this inhibitory action of the vagus than are normal hearts. One naturally searches for a common cause for the very similar phenomena that appear in all these attacks; but no such common cause has yet been discovered. It is possible to explain the attacks of some patients by vagal influences either on conductivity or contractility, but this still leaves a very large number of the attacks unaccounted for.

The patient, now aged 61, from whom the tracings were obtained came first under my care three years ago, and was at that time shown by me to the Clinical Society (*Clinical Society's Transactions*, 1905, Vol. XXXVIII, Case 1). Her history was that she had been quite well up to one month before coming to the Hospital, but that during the previous month she had had, three or four times a week, attacks of giddiness of sudden onset, and that in these attacks she frequently fell and sometimes became convulsed. She was admitted into the Hospital, and was found to have old syphilitic scarring of the pharynx, some loss of bone from the nasal septum, and marked ozaena. The heart was always beating between 30 and 40 to the minute, and no intermediate sounds between the large beats were heard. The arteries were decidedly thickened, and occasionally some albumen was found in the urine. After leaving the Hospital the patient was lost sight of for over two years; but she subsequently stated that she had been fairly well in the interval, and free from attacks. She returned to the Hospital in July, 1907, because she had had several of her attacks in the previous week. Her general condition was the same as when she was previously in the Hospital and she again rapidly improved with rest. A radial and jugular tracing taken at this time showed that there was complete heart-block, the auricles and ventricles beating quite independently of one another. The pulse-rate was usually about 36. An examination was made with the X-rays, but it was not found possible to distinguish the beating of the auricles.

She remained in fair health, and had no further attacks until April 4, 1908. The attacks then came on again with increasing frequency and severity until April 7, on which day she had about two dozen, some of them slight, but many of them very severe with violent convulsions. She was brought up to the

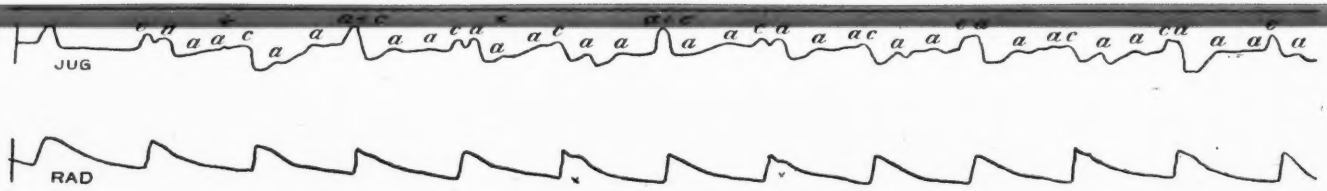



FIG. 1.

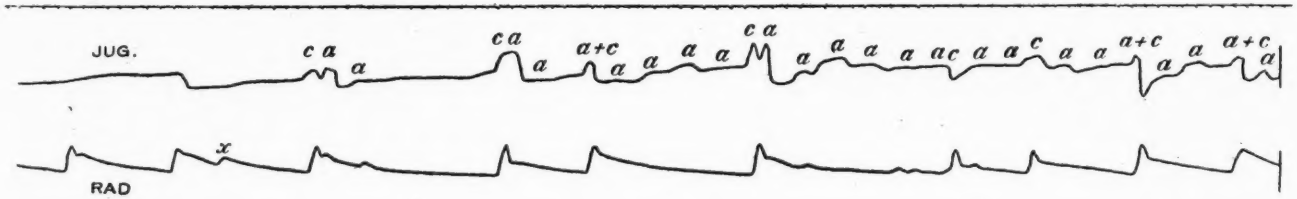



FIG. 2.

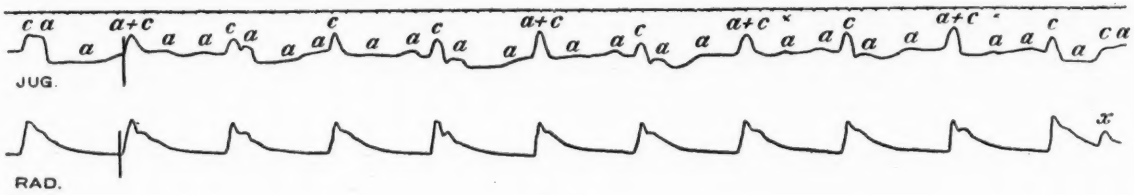



FIG. 3.

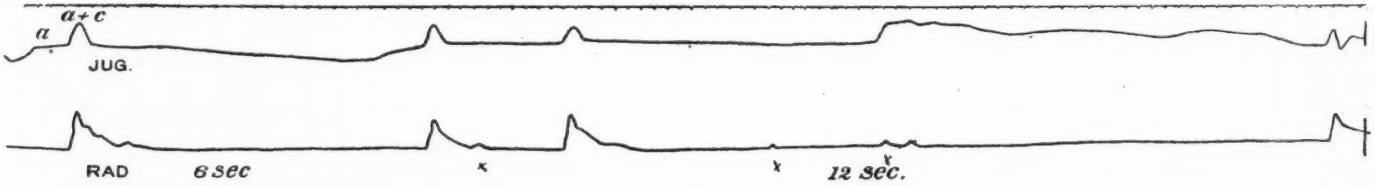



FIG. 3*a* (tracing taken directly after Fig. 3)

Hospital on this day and had three attacks in the Out-patient Department. One of these attacks started with a loud cry, then the patient became unconscious and violently convulsed. No pulse could be felt in the radial, and no sound heard over the heart for a space of 85 seconds, during which the convulsions continued. The breathing continued throughout the attack, except for a short period in the middle, when for a moment I thought that she had died. The pulse returned quite suddenly, and almost at once the patient became conscious again. This attack occurred just as the recording apparatus had been removed from her wrist and neck, but records of slighter attacks were obtained subsequently.

In Fig. 1 it is evident that the auricles and ventricles are beating independently of one another, or, in other words, that there is complete heart-block. The ventricles are beating at 36 to the minute, while the auricular rate is 96 (i. e. 8 auricular beats to 3 ventricular). The position of the auricular wave $a$ compared with the carotid wave $c$, is shown in the upper tracing from the jugular vein, and it is seen how this varies with successive beats, every third carotid wave coinciding with an auricular wave $(a+c)$. In Fig. 2 are shown some periods when the ventricles cease to beat, the longest of which is 3 seconds; during these periods the auricles apparently continue to beat regularly. Some small waves appear in the radial tracing during the ventricular cessation, the origin of which is obscure: they may be due to the auricles, but if so the rhythm of the auricles is altered during the ventricular rests. About 15 minutes later the patient, as shown in Fig. 3 $a$, had a more prolonged attack. In this for over 20 seconds only 2 ventricular beats occurred, and there was an interval of 12 seconds without a beat. In the tracing from the neck there is here no sign of any auricular beats, but this, I think, is accidental. It was always very difficult to get satisfactory jugular tracings from this patient, and in several other parts of the tracing, which was taken continuously for about 45 minutes, there is no record of the auricular contractions, doubtless because of faulty application of the recording receiver. It is probable, therefore, that the auricles continued beating. In the radial tracing there are some small waves, like those in Fig. 2, which are possibly due to the auricles, though they occur very irregularly. During this attack the patient's expression became rather set, but she apparently did not lose consciousness and was not convulsed. She herself described it as a slight attack.

In complete heart-block the pulse rate is said to vary very little, but it was noticeable with this patient during the next 3 days that the rate differed considerably at different times, the most rapid being about 50 and the most infrequent about 24 per minute. With rest she soon got better; there was only one severe attack on April 8, and only one slight one (see Fig. 6) on April 9. After this she had no further attacks, and the pulse rate remained nearly constant at about 30 per minute, though occasionally an extra-systole was noticed.

Throughout nearly the whole of April 9, a remarkable irregularity of the

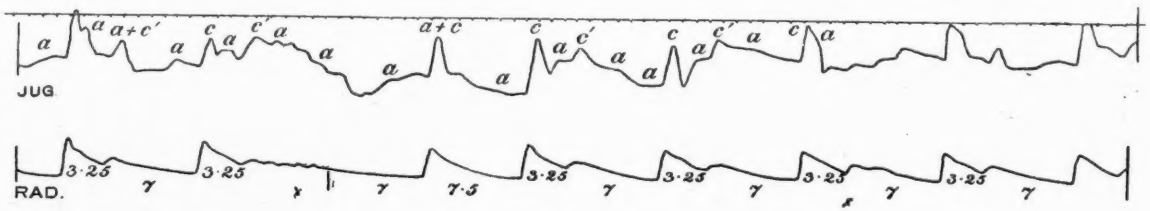



FIG. 4.

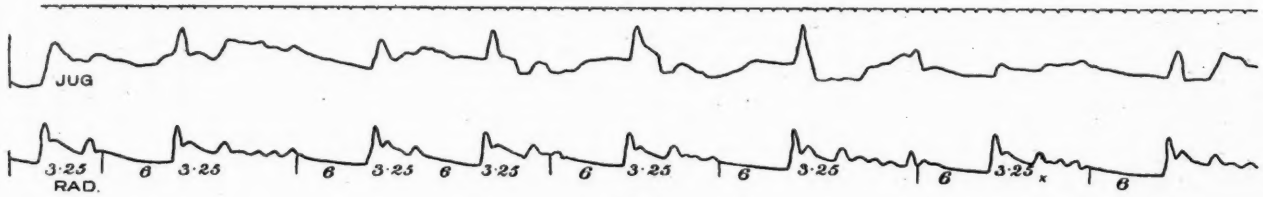



FIG. 5.

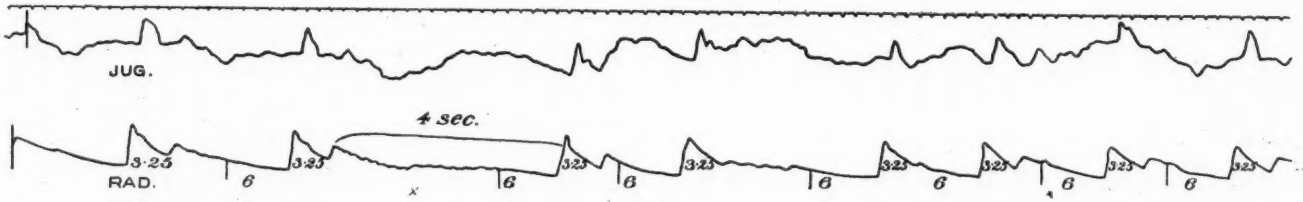



FIG. 6.

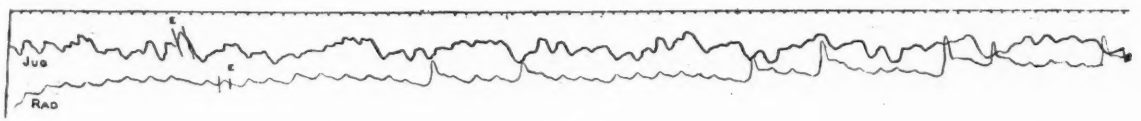



FIG. 7.

pulse was present, each large beat being followed by a smaller one. In the afternoon I took a tracing, lasting nearly an hour, and found that this peculiar type of pulse was continuous throughout. In Fig. 4 it can be seen that the second small beat always occurs 3·25 fifths of a second after the large beat, and that the small beat is always followed by a pause of 7 fifths of a second. This means that there is here a true bigeminal action of the heart, the two beats being coupled together with always the same interval between them. In one place in the tracing the second beat is absent, and one can find the normal interval between two large beats, which comes out as 7·5 fifths of a second. This is practically equal to the interval regularly occurring after each small beat; the reason for its being a little longer than the 7 fifths of the other intervals is that the small beats are conducted to the periphery rather more slowly than the large beats, and so have a shorter interval after them in the radial pulse, though the intervals at the heart would be the same. In this case there is then a complete absence of a compensatory pause after the premature systole; this is in keeping with the ventricular origin of the stimulus which necessarily prevails with complete heart-block. In one place the second of the coupled beats is followed by five more very small rapidly succeeding beats, after the last of which there comes the normal pause of 7 fifths of a second. In other parts of the tracing these rapidly recurring beats after the second of the bigeminal pulsations are more conspicuous (see Fig. 5), and sometimes the number of such beats is very numerous. On every occasion, however, after the last of these small beats, there comes an interval, which is equal to the normal interval between two large beats. In Fig. 6, for instance, where the ventricles are beating more rapidly, the interval is 6 fifths of a second. This irregularity of the ventricle naturally affects the tracing obtained from the neck and makes it difficult to interpret, but apparently the auricles continue beating regularly (see Fig. 4).

Wenckebach (*Archiv f. Anat. u. Physiol., Physiol. Abtheil.* 1906, p. 297) has called attention to this peculiar type of heart action as occurring in cases where the auricles and ventricles are completely dissociated from one another, and has collected from his own records and from medical literature twelve cases which exhibited it, in most of which there was clear evidence of complete heart-block, whilst in others this condition was probable. This type of rhythm has more than an academic interest, for Wenckebach points out that the small beats of the ventricle here described would be insufficient to fill the arteries, and that the occurrence of a sufficient number of them would lead to cerebral anaemia and its consequences. In one case his patient had two attacks of the Stokes-Adams type, of which he gives tracings, showing that the attacks were due to this peculiar type of rhythm and not to a cessation of ventricular beats. In the more severe of these two attacks, only these inefficient ventricular beats occurred for a period of over ten seconds, and towards the end of this time the patient became convulsed. In my patient, too, what she described as a very slight attack took place whilst the tracing was being taken. The period that then ensued without any efficient ventricular beat was approximately four seconds (see Fig. 6), and

in this period there are about a dozen small beats. One must now consider whether the attacks in Fig. 2 and the more severe one in Fig. 3 may not have been of this nature rather than due to an actual cessation of the ventricular beats. In favour of such an explanation is the tendency, shown at *x* in both tracings, to a bigeminal action, and the occurrence of very small waves during the supposed quiescent period of the ventricles. These small waves, however, in Fig. 2 come close up to the succeeding large wave; and the regular pause, corresponding to the normal pulse period, is absent, while in Figs. 4, 5, and 6 its presence is conspicuous and invariable. I think, therefore, that in Figs. 2 and 3 there has been a real stoppage of the ventricles as in the more usual type of the Stokes-Adams attacks.

Wenckebach in discussing these cases quotes Gaskell's description of an experiment in which stimulation of the auriculo-ventricular ring of muscle produced a series of contractions, while stimulation anywhere else only brought forth single beats. The representative of the auriculo-ventricular ring of muscle in higher animals is the auriculo-ventricular bundle of His and its branches, and it seems possible that under certain circumstances stimulation of this bundle may result in a series of beats in human beings. Beyond the occurrence of this type of rhythm in complete heart-block we do not, however, know what the propitious circumstances are. It is noticeable that even in complete heart-block this rhythm is exceptional and only lasts for a few days at a time at the most.

It is of interest and importance to note that a very similar type of cardiac rhythm, where there is a rapid succession of very small beats between larger ones, tends to develop in those cases of permanently irregular heart action with a purely systolic venous pulse to which Mackenzie has given the name of 'nodal rhythm'. In these cases the auricles either contract simultaneously with the ventricles or do not contract at all; and so the stimulus for the ventricular contractions comes either from the auriculo-ventricular band or from the ventricles themselves. In respect, therefore, of the origin of the stimulus these cases resemble complete heart-block, and the rhythm may be due to the same causes. An illustrative example is given in Fig. 7. This tracing was taken from a man of 60, whose disease was diagnosed as degeneration of the cardiac muscle. He had considerable dyspnoea on exertion, his heart was somewhat dilated, and his pulse persistently irregular. A comparison of the radial and jugular records in the tracing shows that the wave in the vein is purely systolic, and there is no trace of any auricular contraction. It is noticeable, however, that, although this tracing resembles Figs. 5 and 6, it differs from them in the absence of the marked bigeminal action.

# RHEUMATIC MYOCARDITIS

By CAREY COOMBS

With Plates 5, 6

*Introductory.* That there is a close relationship between acute rheumatism and cardiac disease has been a matter of common knowledge for nearly two hundred years; and with last century's researches into the structural changes due to disease came a clearer understanding of the type and position of the morbid processes of rheumatic origin seen in the heart.

A productive inflammation, associated with deposition of fibrin, selecting such easily examined tissues as are the serous envelopes of the heart wall, could not fail to attract much attention. Indeed, so important did these changes appear to the earlier pathologists that almost no notice was paid to the condition of the myocardium (except, of course, to such changes as were obviously secondary to the mechanical embarrassments of the circulation which result eventually from endocarditis and pericarditis), until about thirty years ago, when the increased practice of microscopy led to an appreciation of the fact that not only the serous layers, but also the muscle itself, might participate in a cardiac inflammation. Since then the various observations that have been recorded fall into two periods. The first of these opens with a paper by Samuel West in 1878 (1), who was followed by Goodhart in 1879 (2), and constitutes the recognition of the existence of myocardial changes in acute rheumatism. It includes the statement by Sturges (3), in his Lumleian lectures, that rheumatism causes a carditis in which all the cardiac structures suffer.

The second period may be said to begin in 1896 with Fisher's proposition (4) that mitral insufficiency, even in rheumatic carditis, is more often myocardial than valvular in origin. Papers by Lees (5) (6) (7) and Poynton (8–12) (20, 21) soon followed, which were of so explicit a character as to attract much attention. At the same time our conception of what should be included in the term 'rheumatism' has widened, and newer methods of physical examination have reminded us that the heart is after all a muscular organ with accessory serous structures; so that it is fitting to speak of this as the period of appreciation of the importance of myocardial rheumatism. It is for the widening of this appreciation that my paper is written.

*Material.* My material has been drawn from 8 autopsies, 7 of which I performed myself. For the other heart I am indebted to Dr. Reginald Miller, Registrar to the Hospital for Sick Children, Great Ormond Street. Six of the patients were under 16 years of age, one of them was a youth of 21,

[Q. J. M., Oct., 1908.]

to whose case I shall specially refer, and the other a girl of 19 whose heart has been thoroughly investigated (I have examined several hundreds of sections from it with a purpose presently to be described). About the rheumatic nature of the changes found I need say no more than that a history of rheumatism or of chorea is accepted as sufficient evidence, in conjunction with the fact that the pericardium, myocardium, and endocardium were inflamed in every case, in varying degree and proportion. Each case was therefore one of pancarditis with a history of a rheumatic event. Several other cases of chronic mitral and aortic disease have also been examined. From time to time I shall also refer to 88 autopsy records of non-suppurative carditis fatal before the age of 16, drawn from the Bristol hospitals.

*Macroscopic changes.* In order to introduce those changes in the muscle in rheumatic carditis which are visible to the naked eye, a short note of an autopsy will suffice.

The boy, aged 8, had been under my care at the Children's Hospital, Bristol, in the out-patient department. About a fortnight before his death he was admitted again (he had been in the wards on previous occasions) because of an increasing dyspnoea. He had, at the apex, systolic and presystolic murmurs. His condition improved perceptibly till about 24 hours before his death, when the dyspnoea increased alarmingly and he became collapsed and pale, with an enfeebled pulse.

I performed the autopsy and found the heart greatly widened so as to extend from the left axilla to a point two inches beyond the right sternal margin. The left lung was thrust aside and compressed at its base, and there were gracile adhesions binding the left pleura to the pericardium. Beyond this there was no evidence of pericarditis. The mitral valve was the seat of a fibrosis which scarcely stiffened its cusps but indicated a previous inflammation, surmounted by a fringe of tiny vegetations of the usual rheumatic type. The other valves were normal. The root of the aorta showed small whitish patches under the endothelium. So far, then, the heart (removed from a boy who for some time had presented symptoms and signs of grave cardiac disorder) was but little altered. But there were changes in the ventricles of the very greatest importance and interest. I have already spoken of the heart as widened; this was due to a great stretching of the ventricles and enlargement of their cavities which expressed itself especially in the transverse measurements of the heart. The left ventricle was probably more enlarged than the right. A measure of the dilatation is found in the size of the auriculo-ventricular rings; the mitral orifice allowed the tips of two fingers, the tricuspid three; that is to say, a boy of 8 had auriculo-ventricular rings practically of the same size as a normal adult.

There was thickening of the ventricular walls: the left ventricle wall averaged half an inch, the right about a quarter of an inch, a real increase in bulk when the stretching of the walls is taken into account. This increase is further attested by the fact that the heart, free from clots, weighed 11 ounces, or as much as that of a healthy adult male.

To the naked eye the consistence of the heart muscle was not changed; but a regrettably imperfect microscopy revealed an interstitial inflammation.

In this case, then, there were three features of interest in regard to the myocardium, namely, dilatation of the ventricles, hypertrophy of the same, and absence of naked-eye alterations in structure. It is better that these features should be enlarged upon before the microscopical data are described.

Dilatation reaches its extreme development when there are pericardial adhesions, associated with valvular sclerosis (particularly of the aortic cusps). The largest hearts are those met with in what constitutes a very definite group of cases. The patients are adolescents and young adults varying from 17 to 30 in age; there is more or less pericardial adhesion, moderate valvular sclerosis with recent inflammation, and enormous ventricular enlargement. Further reference will be made to such a case later. Though in such cases dilatation reaches its maximum, yet lesions of the accessory layers are not essential to its production. Any poison damaging the cardiac muscle-cells allows of over-distension of the ventricle during diastole, and hinders it from recovering itself. Dilatation, then, is not a surprising phenomenon in a ventricle the seat of rheumatic myocarditis.

Hypertrophy is incontrovertibly present even when there is no obvious mechanical hindrance to the work of the ventricles such as we are accustomed to use as an explanation of ventricular hypertrophy. As examples we have only to turn to the case already described and to another examined after death by myself, that of a boy of 7 who had a barely perceptible pericarditis, a corresponding degree of mitral endocarditis, a heart weighing 8 ounces, or more than double the normal weight at his age, and a left ventricle wall half an inch thick. Both these children had had several attacks of rheumatism.

In order further to establish this fact of 'idiopathic' hypertrophy in rheumatic carditis, I have tabulated the weights of the hearts and the ages of the patients, in fifty fatal cases where both are recorded, in four classes. These patients were all under 16.

TABLE I.

| Nature of cases. | Number. | Average age. | Average weight of heart. |
|---|---|---|---|
| I. Those with pericardial adhesions . . . | 23 | 11 | 14·65 oz. |
| II. Those with valvular sclerosis sufficient to cause mitral obstruction or aortic incompetence . | 4 | 14·5 | 12·12 oz. |
| III. Those with both pericardial adhesion and valvular sclerosis . . . . . | 3 | 15 | 31 ·6 oz. |
| IV. Those with neither of these lesions . . | 20 | 11·5 | 9 ·9 oz. |

The great excess of weight in Class III is due to the fact that one of the hearts weighed 49 ounces. This table shows many points of interest; for the moment, however, it is enough to say that while the largest hearts are those in which the enlargement is at any rate mainly due to mechanical embarrassment by lesions of the serous layers, there remains a group in which there is a definite increase in the heart's weight (to nearly twice its normal weight at the average age) with no more than a few tags of fibrin on the pericardium and a moderate thickening of the valves—changes probably negligible as far as their interference

with systole is concerned. How, then, is this hypertrophy caused? That it is not merely an increase in weight due to inflammatory exudation will be readily acknowledged by any one who has examined sections of the ventricle wall under the microscope.

There are two possible hypotheses, which might also be brought forward to explain the similar change found in the beer-drinker's heart. The first is that the hypertrophy is directly compensatory to the dilatation already referred to, a response, in fact, to the increased burden of blood to be lifted at each systole. This, however, is hard to picture; it can scarcely be that cardiac muscle already damaged by deprivation of its blood supply can yet so take advantage of this same blood supply as to multiply its elements. The other hypothesis, which will be developed in a later paragraph, supposes some 'direct' effect of the rheumatic poison upon the cardiac wall in addition to, and perhaps alternating with, that purely destructive action by which dilatation is made possible. That the increased weight is in some way due to the toxaemia and not merely to intramuscular exudation of inflammatory origin was very acutely suggested by Goodhart (2) nearly thirty years ago. Such hypertrophy, I may add, is easily demonstrable clinically, and is most definite in those who have been the subjects of repeated rheumatic outbursts.

The actual naked-eye appearance and the consistence of the cardiac muscle are but little altered. In the 88 autopsy records various comments are made (apart from remarks as to dilatation or hypertrophy). The muscle is described as 'normal' several times; in others it was 'flabby', 'soft', 'pale', 'dirty red', 'speckled', 'fatty', 'browner than normal', 'friable', 'showing tiny white dots and patches'. In twenty-one cases it is adversely commented on. It is, however, so well known that a myocardium healthy to the naked eye may reveal grave alterations under the microscope, that there is no need to say more than that several of the cases seen by myself presented a normal macroscopic appearance, but that I have never in any single case failed to find unmistakable evidence of myocarditis under the microscope. In my own cases tiny areas of fatty change were several times seen beneath the ventricular endocardium. Cicatrices such as Fisher (13) described were not detected with the naked eye.

*Microscopic changes.* Turning next to the morbid histology of rheumatic myocarditis, there are lesions of the parenchyma and lesions of the interstitial tissue. The muscle-cells, like other specialized cells subjected to the action of a poison, show changes which are degenerative rather than reactive, and are therefore not, strictly speaking, inflammatory. In the connective tissues, however, there is a definite response to irritation, a response of a peculiarly interesting type, to which the greater part of my attention has been devoted. Before entering upon a description of these changes, however, those met with in the cells themselves should be detailed. Let me first repeat that in every case examined evidences of myocarditis have been found; and this is, I believe, the experience of those other investigators who have examined numbers of cases.

In the cells the most definite indication of morbid change is the intracellular deposit of fat. To demonstrate this, Sudan III was at first used; but in later cases Scharlach R (Herxheimer's acetone method) has been used with admirable results. The stain is sharper and more brilliantly red than Sudan III. In eosin preparations vacuoles are seen in the cytoplasm representing spaces from which the fat has been dissolved out in the hardening processes. The earliest appearance of fat is close to the nucleus where minute droplets form. These are added to centrifugally, by other droplets forming in rows along the longitudinal fibrillae. These droplets tend to assume a quadrilateral shape, probably owing to the nature of the boundaries by which they are contained. They do not encroach on the perinuclear lacuna. Gradually the process extends till rows of fat-drops stretch from end to end of the cell, those in the centre being still the largest of all. Finally, the cell may appear almost entirely filled by fat. Transverse and longitudinal sections of the fibres alike show this centrifugal spread of the fat-forming process. With regard to the general distribution of this alteration of the fibres several statements may be made.

The more vascularized parts are those which suffer most, so that in the muscular bundles the peripheral cells show changes earlier and more definitely than those which lie centrally. That is to say, the cells in immediate contact with the larger capillaries are more diseased than those more remote; occasionally areas of fatty change border on the arterioles. Patches of red, scattered through the ventricular wall, form a striking feature in Scharlach R preparations. They are discrete in the more central parts of the myocardium, and thickly aggregated under the pericardium and endocardium. The left ventricle shows a greater degree of disease than the right; and the tips of the papillary muscles are visited with especial severity. No fatty change was discovered in the auricular walls. The interventricular septum is also relatively immune.

Of other intracellular changes there is little to be said; fatty change has seemed to constitute so satisfactory an index of morbidity as to render multiplication of histological methods rather a waste of time. I have in several instances made methyl violet preparations, but have so far observed no amyloid degeneration such as Beattie (14) has described in various organs in acute rheumatism. Thick fibres with coarse nuclei are commonly observed; but it is probable that is merely an evidence of the hypertrophy already alluded to. In one heart I have noted what appeared to be an increase of the pigment deposit always present in the space at the poles of the nuclei; these cells are not atrophic, but the part was the seat of hyperaemia—a fact to which further reference must be made. Segmentation has not been noticed in any case.

The interstitial changes may be considered in two groups, the 'submiliary nodules' and areas of leucocytosis. Submiliary nodules were first described as such by Aschoff and Tawara (15), and subsequently by Geipel (16); but the fact of their occurrence was undoubtedly registered by Poynton (9) in a

figure published in 1899, though he gave no detailed description of their histology. They consist of rounded or fusiform areas, formed by large spindle-shaped cells, lying in the intermuscular trabeculae of connective tissue. I have seen them in five hearts; in two hearts I have no record of their presence, and unfortunately the slides are lost. In another heart there were many scars, the result of a former myocarditis. In this case there was no evidence in any part of the heart of active carditis. Only one has been measured (by means of serial sections of known thickness). This was a fusiform nodule lying in the subpericardial fat in apposition to an artery, and could be measured from pole to pole as about 400 $\mu$ in its greatest length. This, I should judge, is rather above the average. Their appearance in the section is striking, since they consist entirely of large cells which stain well.

These cells are much larger than the fibroblasts of ordinary inflammatory reactions; to which in other respects they most closely approximate. The outline of the cells is usually fusiform, but not always; it seems as if this were due to the position which they occupy, compressed in connective-tissue planes. In those nodules where fibrous tissue is particularly plentiful between the cells they are lengthened out to an extreme degree; they are, however, sometimes rounded. The nuclei are often multiple, in some nodules in as many as half the cells. I have counted seven nuclei in one cell, but not more. In cells with rounded outline the nuclei lie chiefly at the periphery, but never as exclusively as in the tuberculous giant-cell. In most of the cells they lie perforce along the longest diameter, since the width of the average cell is only great enough to accommodate one or two nuclei abreast.

The chromatin substance is in most instances seen only as a sharply defined margin and a small central mass or masses; the rest of the nucleus, therefore, takes no stain and gives a curious appearance to the cell, as if it contained a large vacuole, or a droplet of some highly refractile substance. In this respect it resembles the nucleus of a plasma cell. Sometimes, however, the network is more plentifully distributed within the nucleus, which then takes the stain more uniformly and has a less characteristic appearance. It is oval rather than rounded, except in some degenerate cells to be noted shortly; some nuclei are triangular or quadrilateral. Mitosis has not been observed. The haematoxylin preparations have proved useful in studying these details, particularly Weigert's iron haematoxylin and Mayer's haemalum.

The cytoplasm stains deeply and with uniformity; it appears to be amphophile, such predilections as it has being in the direction of basic dyes. Cells stained with methylene blue, thionin, methyl violet, and other members of this group, give the vacuolated impression already mentioned with peculiar force, since the scanty sharp staining of the nuclear chromatin contrasts strikingly with the uniformly and deeply dyed cytoplasm. The largest of these cells are as large as, or larger than, ordinary myocardial cells. In a few instances a row of five or six quadrilateral cells arranged end to end is a striking feature of the nodule.

In addition to these cells there are others at the periphery of the nodule, of a more ordinary type, namely, plasma cells and leucocytes chiefly of the mononuclear kinds. These cells are, however, limited almost exclusively to the periphery, leaving the other larger cells in sole possession of the centre. This is indeed the most characteristic feature of the nodule, that its central portion is composed of nothing but these large fibroblastic cells, loosely packed in a fine fibrillary matrix. Each cell seems to lie in a kind of lacuna of its own: but it has no reticulum around it such as is seen about the giant-cell of tuberculosis.

It is for the determination of the distribution of the nodules within the cardiac wall that the full examination of the heart (mentioned earlier in this essay) has been undertaken. The following definite statements may be made about this one heart, which will be confirmed or modified by similar examinations of other hearts :—

(*a*) The nodules are very often immediately related to arteries. Sometimes a longitudinal section of an artery reveals a chain of nodules imperfectly separated from each other; in others, again, a sleeve-like nodule is seen enveloping the vessel for a considerable part of its course. Transverse sections of arteries exhibit varying types of nodule arrangement; sometimes the nodule, lying mainly on one aspect of the vessel, sends processes in both directions to embrace it, forming a sort of signet-ring. At others the nodule is semilunar, enwrapping half or more of the vessel's circumference. In others, again, there may be two nodules, one at each pole of the circumference of the vessel. They appear to arise usually from the periarterial connective tissue, but sometimes from the tunica adventitia of the artery itself; and once nodule formation was found in the media of an artery, pressing into the lumen of the vessel and partially occluding it.

(*b*) At first my impression was that the nodules were more frequently found just under the serous investments than in the depths of the cardiac wall; but fuller investigation proves that the reverse is the truth.[1] Nodules are found in numbers, just under both serous layers, especially in the subpericardial tissues; but they are most thickly sown in the central parts of the myocardium. Sections of the auricular walls have so far discovered almost no nodules except under the endocardium close to the auriculo-ventricular ring.

(*c*) In the right ventricle they are scanty; none could be seen in a large papillary muscle, and very few in a portion from the wall half-way between apex and base. The most productive sections were from a block of tissue close to the apex; next to this came that portion of muscle bordering on the fibrous ring giving origin to the tricuspid flaps.

[1] The mode of estimation of the relative frequency of the nodules has been to take representative portions of the cardiac muscle, and to make series of sections from these with measured intervals between the sections. Each section is then examined under a 3-Leitz objective and a 2-Leitz eyepiece, the number of nodules being counted field by field. The average number of nodules per field is then calculated. In one such field there were six nodules, and four or five have been repeatedly seen.

(*d*) The interventricular septum contains but few nodules; none were found in relation with the auriculo-ventricular band of His, but I hope to investigate this more fully in other hearts.

(*e*) The wall of the left ventricle contains the bulk of the nodules. The least affected part was a large papillary muscle; the columnae carnae near the apex are relatively immune. The nodules were sown most thickly at the origin of the aorta, at the apex close to the septum, and at the insertion of the ventricular wall into the fibrous ring of the mitral valve. In other parts of the wall there were many nodules, but not so many as in the parts named.

(*f*) Although this paper deals only with the cardiac muscle, there are one or two observations dealing with other parts of the cardiac wall which are of sufficient importance to call for notice. Nodules were not found in the depths of the fibrous tissue which forms the scaffolding of the auriculo-ventricular rings. They are, however, to be seen in the valves near their free edges, and in the chordae tendineae, at some depth from the endothelial surfaces. They are quite numerous in one valve which had become thickened and vascularized by previous inflammations. I have twice seen them in valves inflamed for the first time. In the subpericardial fat a few were observed; in the pericardium itself a considerable number of the large cells described above are scattered about in it, just under the layer of fibrin, and gathered together in isolated patches to form definite and unmistakable nodules.

Of the nature and ultimate destiny of these nodules a little may be said. Reasons will be given later to show why they should be regarded as a highly characteristic form of connective-tissue reaction to irritation. As to their fate, they appear to end in one of two ways: (*a*) cloudy swelling, and (*b*) cicatrization. This latter is the commoner mode of termination. Strands of fibrous tissue develop between the cells (not apparently *from* the cells), which become lengthened out till the length may be six or eight times as great as the maximum breadth; their multinucleate nature and the staining reactions remain unchanged for a time, but gradually the nuclei take the stain less sharply, the cytoplasm becomes cloudy and develops a greater affinity for acid dyes, so that the cell eventually appears as an eosinophile homogeneous mass set in a network of newly-formed fibrous tissue.

In several hearts these cicatrices were seen without any of the acuter changes being present. They were particularly in evidence in one case of chronic rheumatic carditis dying gradually and not acutely from the effects of a mechanical obstacle to the circulation. There were dense pericardial adhesions and sclerotic changes in the mitral valves, but no certain evidence, either microscopically or to the naked eye, of acute inflammatory change in any of the cardiac structures. Parts of the left ventricle wall showed many of these scars; many of them were periarterial; they were as a general rule denser in the centre, sending out radial fibrils of connective tissue between the surrounding muscular bundles. They were therefore irregularly star-shaped, and occasionally attained a very considerable size. They were exactly like those in which in the

other hearts the final stages of the nodule process could be detected. The other hearts exhibiting cicatricial changes were from cases of chronic valvular disease succumbing to their mechanical disadvantages.

Sometimes some or all of the cells of a nodule are seen in a condition of cloudy swelling. The cell and its nuclei are less easily distinguishable and become globose. A number of the large cells present in the valves seemed to be in this condition.

The other interstitial lesion of importance is leucocytic infiltration. Aggregations of leucocytes are to be seen in various parts of the cardiac wall; they are sometimes of considerable size, and generally perivascular in situation, spreading between the muscle fibres. They are to be seen especially in the papillary muscles, and also in the subpericardial fat. They appear to avoid rather than to associate with the nodules, and differ in type from the scanty leucocytosis which surrounds these latter lesions in that they show a preponderance of polymorphonuclear cells. It seems likely that these infiltrations are in a large measure due to passive oedema rather than to active inflammation.

Before closing this already lengthy description of lesions, a word remains to be said as to the vascular lesions seen. The coronary arteries are, as has been said already, frequently the seat of nodular periarteritis; allusion has also been made to a mesarteritis of a similar type. In one heart a spot of endarteritis was seen, but this was of an ordinary type, namely, a focus of small-celled infiltration. The capillaries are distended, as Poynton noted in his earliest papers. It seems proper to allude at this point to the constant occurrence in rheumatic carditis of patches at the root of the aorta appearing whitish-yellow through the endothelium. Microscopically these prove inflammatory. Unfortunately my sections were destroyed before the exact nature of nodule formation was appreciated.

I now propose to discuss the importance of the lesions described under two headings. First, there is their aetiological significance to be considered; and secondly, their influence upon the cardiac functions.

*Pathogenesis of lesions.* In order that we may from a study of the foregoing facts gain fresh light on the pathology of rheumatic carditis and of rheumatism in general, the various lesions must be discussed seriatim.

The submiliary nodules afford much food for thought. That they are inflammatory in type cannot be doubted; such cells as I have described were figured by Ziegler (17) in his description of the cytology of plastic inflammation, and are found scattered about in small numbers in most reactive foci undergoing cicatrization. Further than this, however, their appearance and position (in localized spots scattered through the myocardium), and especially the presence of a large proportion of multinucleate cells, lead one to suppose that they represent the reaction of the connective tissues to an infection rather than an intoxication only, and that the infective agent itself comes in contact with the tissues at the points where the nodules form.

So far, however, my work has not produced any convincing proof of this

suggestion in the shape of bacteria in the nodules; this is to be ascribed rather to unsuitable material than to anything else, since none of my hearts have been examined within a sufficiently short interval after death. It may, however, be taken as highly probable that these nodules represent the points of impact of the infective agent into the connective tissues of the cardiac muscle.

Next, it is to be noted that although cells such as constitute the nodules are in no way characteristic of the rheumatic as contrasted with other fibroblastic deposits when considered singly, yet so far as the myocardium is concerned it may be safely said that in no other inflammation do we find aggregations consisting of nothing but large fibroblasts, a considerable proportion of which are multinucleated. I have examined a number of other hearts from cases of pneumonia, malignant endocarditis, suppurative myocarditis, pneumococcal pericarditis, acute pyogenic aortitis, dysentery, &c., without finding anything at all like a nodule; and Aschoff and Tawara (15) after a much wider search were enabled to identify the nodule solely with the rheumatic form of carditis.

Yet stronger evidence in favour of regarding the nodule as highly characteristic of rheumatism is yielded by the fact that similar nodules are seen in the depths of inflamed valves in rheumatic carditis. As this is rather outside the scope of the present paper I need only copy the notes made in regard to sections of valves from two different hearts. In the first case the mitral valve was scarred and thickened by previous attacks, and there were also recent pin-head vegetations. 'The section shows general nodule formation in the deep part of the valve; there are about six nodules more or less separated from each other by defined belts of round-celled infiltration. This infiltration is, however, apparently not an essential feature of the nodule, and scarcely ever penetrates into its deeper parts.

'The nodules show the same structures as in the myocardium, that is, an aggregation of fibroblastic cells, a large percentage of which are large and multinuclear. Many of these seem to be in a condition of cloudy swelling. The valve is much vascularized; each nodule is as a rule near a blood-vessel.' In the other case the mitral valve was suffering its first inflammation. 'The valve contains one group of large cells at the attachment of a chorda tendinea, another actually within a chorda, and another in the depth of the valve near its tip. The cells lie in lacunae; two of them had six nuclei each.' What were probably nodules were also found in an aortic valve in its first inflammation.

Too much stress must not be laid on these observations till examinations of other valves, normal and diseased, have been made; but they are at least highly suggestive. Of similar significance is an examination of the histology of a subcutaneous rheumatic node removed *intra vitam*; here I am indebted to Dr. Dunkley for the beautiful sections which he allowed me to examine. The node was in the fibroblastic stage; that is to say, the precipitation of fibrin described by Poynton and Still had occurred, and the fibrin, though still present, was rather overshadowed by the striking picture of productive inflammation.

In one or two spots, but particularly in one, the appearances under a 4-Leitz eyepiece and $\frac{1}{12}$-in. objective were noted as follows: 'The section shows plasma cells, and fibroblasts of all types and sizes. The largest are seen to be multinucleated, some containing six nuclei, and in length $\frac{1}{4}$ to $\frac{1}{3}$ the diameter of the field. These constitute from $\frac{1}{2}$ to $\frac{1}{5}$ of the cells seen. They lie in lacunae as in the valves, but fitting tighter. Actual aggregations of such cells only occur (that is to say, they are concentrated only) in some patches; such patches are not easy to pick out, because they so closely resemble the general cellular background.'

In the pericardium immediately beneath the layer of exuded fibrin, there is a fibroblastic zone exactly like that of the subcutaneous node; in this zone several very definite nodules have been seen of a precisely similar nature. One such nodule was situated at a little depth from the fibroblastic zone at the junction of the pericardium proper and the subpericardial fat. It is clear, therefore, that in the cardiac valves, in the connective tissue of the cardiac muscle, and in the subcutaneous tissues a peculiarly definite type of connective tissue reaction to rheumatic invasion can occur. How far is this type characteristic? This of course needs to be answered by wider experience to be gained by further investigation.

One other lesson of importance is taught us by these nodules, namely, that the heart is in rheumatism invaded by way of the coronary arteries, judging from the close relations between them and the nodules. This shows why rheumatism produces a pancarditis. In my 88 autopsy cases the endocardium was visibly inflamed in 80 instances, the pericardium in 67; and, as has already been stated, in every case adequately examined the cardiac muscle is found to be inflamed, not only where it touches the serous layers, but also in its depths. This fits in perfectly with the periarterial distribution of the nodules, and also with the presence of similar nodules in the depths of the cardiac valves. Incidentally it may be remarked that this latter fact is convincing testimony to the truth of the belief that acute endocarditis begins in the depths of the valves and not on the surface, is in fact centrifugal and not centripetal. Again, it is of interest in relation to the constancy with which inflammatory patches are seen in rheumatic carditis at the root of the aorta, an area which is supplied by end branches of the coronary arteries. Finally, compare the distribution of the nodules with that of the abscesses in a case of pyaemic myocarditis—three in the wall of the right ventricle, ten in that of the left, and three in the septum ventriculorum.

Of the areas of leucocytosis little need be said. That they represent spots of passive oedema is probable, for they occur in the heart wall in most cases of cardiac failure; they do not correspond in distribution with the submiliary nodules, and they occur in various places where oedema is likely to be found, as, for example, in the areolar tissue around the root of the aorta. That the fatty change is in large measure due to the action of the rheumatic poison upon the metabolism of the cell is almost surely true. There is no need to discuss the

nature of the metabolic change except to say that the writer accepts as a settled fact the theory which ascribes intracellular fat not to degeneration of protoplasm so much as to malassimilation by protoplasm. It is very unlikely that each cell is visited by the infective agent itself: reasoning by analogy from diphtheria and alcoholism there is no need to postulate anything but a general flooding of the myocardial capillaries with some toxin. Where this is formed, and what its nature, are matters for conjecture; it is not unreasonable to suppose that the seats of manufacture lie in the interstitial nodules, as these are probably the points at which the micro-organisms are cast into the cardiac tissues. Support is lent to this conjecture by the general agreement between the distribution of the nodules and that of the fatty areas; in both instances the left ventricle suffers more than the right, the interventricular septum is relatively unharmed, and the auricle wall still more fortunate. There is, however, one rather interesting discrepancy. In the tips of the papillary muscles fatty change is very abundant, but nodules are scarce. Is there anything by which this contradiction may be accounted for? Probably by the fact that in the papillary muscles there is, as already stated, much passive hyperaemia and leucocytosis. In the heart of a patient dying after years of cardiac symptoms due to extreme mitral constriction, the same limitation of fatty change to the ends of the papillary muscles was noted, but of a more diffuse type than in active carditis. It seems then that in estimating the distribution of the rheumatic virus the interstitial nodules may constitute a more reliable index than intracellular fatty change, since the latter is probably in part dependent on the venous stasis incidental to cardiac failure. In the case of adherent pericarditis where cicatrices were so prevalent, fatty change under the pericardium was well marked in spite of the absence of acute phenomena; there were hypertrophy and evidences of passive hyperaemia, which may account largely, if not wholly, for the presence of fat in the cells in visible quantities.

Dilatation of so extreme a degree as we sometimes see in rheumatic carditis is scarcely to be referred to anything but myocardial change when it is seen occurring in absence of valvular or pericardial disease other than the most trivial inflammations. It is, however, not fully accounted for by the fatty change, which at its worst is but moderate. It is therefore needful to suppose the existence of cellular change less gross than the accumulation of fat and therefore less certainly demonstrable. Under the influence of a large dose of the virus the ventricles may stretch so rapidly that their increase is clinically perceptible; but that enlargement of the ventricles which constitutes so striking a feature of quiescent rheumatic carditis is probably referable to the action of smaller and repeated doses. It is interesting to compare the effect of rheumatism on this, a specialized cell, with that observed when it attacks that other specialized tissue, the cortex cerebri. In both cases it is remarkable that with tissues so delicate, effects which clinically at all events seem so severe, recovery may be so complete. Many cases of mitral stenosis must have been through this stage of ventricular dilatation; and yet in how few of those dying in later

years is there much enlargement of the left ventricle! No less striking is the apparently undamaged condition of an adult brain which in childhood suffered repeated attacks of chorea.

The hypertrophy of the ventricle already described is a particularly interesting phenomenon. It has already been shown that it is not entirely explained by the usual mechanical causes of hypertrophy, but that even where these are absent hypertrophy may exist in a considerable degree. I have also suggested that this is probably due to some 'direct' action of a toxin on the heart. This 'direct' action is not improbably in the nature of periodic over-stimulation. The evidence in favour of this hypothesis is as follows:

1. The action of the heart during active rheumatic carditis is rapid, tumultuous, and violent. This is a common clinical fact and one of considerable practical value as an indicator of active cardiac inflammation. Only this week a child came to my out-patient room with rheumatic synovitis and such a heart, beating 120 times per minute.

2. One of the characteristic features of rheumatism is its repeated recurrence; for example, a child of ten, one of my out-patients, in five years suffered nine attacks of chorea.

3. Certain toxic substances by inducing constant or frequent over-action of the heart lead to its hypertrophy; for example, hyper-thyroidism, tobacco, alcohol, and probably tea. Whether such substances act immediately on the heart muscle or by way of the accelerator fibres does not particularly matter as far as this paper is concerned. Here reference may be made to the recent work of Goodall and Mitchell (18) in the action of formates on the heart, which shows the directly poisonous effects of these salts upon the myocardium. Formic acid is excreted in excess in rheumatic fever, and is elaborated in the cultures of Poynton and Paine's Micrococcus rheumaticus (19). But whatever may be the poison at work in rheumatic carditis, it seems plausible to hold that by repeated small doses hypertrophy is established together with dilatation, while too frequently there arrives an excessive dose by which unopposed and fatal dilatation is caused.

The foregoing paragraph may be summarized in a picture of the genesis of rheumatic carditis. It seems that the lesions are produced by an infective agent reaching the cardiac muscle by way of the coronary arteries, and selecting especially the wall of the left ventricle. A highly characteristic reaction is seen in the connective tissues thus attacked, not only in the cardiac muscle but also in the valves, which tends eventually to fibrosis. Poisonous substances are disseminated from these foci throughout the cardiac muscle, upon which they exert a deleterious influence. This reveals itself in the form of ventricular dilatation and is also probably responsible for the hypertrophy which occurs independently of mechanical causes; while microscopical proof of the same poison is yielded by the presence of fat within the cells.

Before passing to a consideration of the effects of rheumatic myocarditis, I venture to remark once more upon the very characteristic cardiac changes just

described; in particular, ventricular hypertrophy without obvious cause, and the formation of interstitial nodules unlike anything met with in other forms of cardiac inflammation. Can the upholders of the 'attenuated pyaemia' theory of rheumatic infection find in these changes any reasonable basis for their hypothesis? Whatever the infective agent may be (and in the opinion of the writer the claim of Poynton and Paine to the discovery of a specific micrococcus has never been overthrown), it is certainly not 'attenuated' while it can cause acute and rapidly fatal cardiac dilatation, nor 'pyaemic' in its effects so long as it excites a peculiar form of fibroblastic reaction without much leucocytosis. There was some excuse for the existence of the term and the idea which it involves so long as the outline of the clinical and pathological features of rheumatism was enshrouded in obscurity. Now, however, that it is gradually emerging into the light of fuller knowledge and becoming more and more sharply defined thereby, it is as unjustifiable to label it 'attenuated pyaemia' as to speak of it as a perverted form of tuberculosis; for its affinities with tuberculosis are very numerous, yet no one would suggest any direct relationship between the two.

*Influence on the Action of the Heart.* There yet remains for discussion the influence of rheumatic carditis on the action of the heart. This influence may be examined, first, as it produces physical signs of cardiac disorder; second, as it proves fatal.

A. *The influence of rheumatic myocarditis on physical signs.* From notes taken (at St. Mary's Hospital, the Bristol General Hospital, and the Bristol Children's Hospital) on 92 cases of rheumatic carditis in patients under sixteen years of age, the following conclusions have been formulated.

There are four main clinical groups into which these cases fall. The principal of these comprises cases of general ventricular enlargement with evidence of mitral reflux. Added to such signs may be evidences of pericarditis, either active or quiescent, with formation of adhesions; these cases constitute a second group. A third includes cases with definite evidence of some deforming valvular lesion, either aortic disease with insufficiency or mitral disease with obstruction. (Of this latter lesion a coarse crescendo presystolic thrill and murmur are accepted as criteria.) In the fourth group are placed cases with a 'malignant' form of endocarditis originating in a rheumatic inflammation of the heart. In my series is included one case of this latter type seen several years before I began to make systematic observations; but though it is not properly within the series, it is mentioned in order to introduce the fact that the class of disease, of which it is an example, exists. The relative proportions of these groups are expressed in the following table:—

TABLE II.

| Class of case. | Number of cases. | Percentage. |
|---|---|---|
| I. Cardiac enlargement with mitral reflux *only* . . . | 69 | 75 |
| II. Pericarditic signs. . . . . | 9 | 9·8 |
| III. Evidence of valvular deformity (aortic incompetence or mitral constriction) . . . . . | 18 | 19·5 |
| IV. Evidence of valvular destruction (malignant endocarditis) . | 1 | 1·1 |

Several cases fall into both second and third groups.

In three-fourths of these cases (which, though numbering less than a hundred, may be taken as representative of rheumatic heart disease in childhood) there were no signs of pericardial disease, aortic valvular disease, mitral stenosis, or ulcerative endocarditis. The signs that characterize this large group will now be detailed, and it will be my endeavour to refer the production of each to disease of the cardiac muscle.

(i) The area of cardiac impulse increases till it may reach from the right nipple to the left axilla, and the impulse itself takes on a peristaltic character; that is to say, it is first seen at the sternal end of the third and fourth left spaces, and travels downwards and outwards to disappear outside the nipple in the fifth or sixth left space. As it reaches this latter extreme an apparent sinking-in is noticed in those spaces where the wave was first seen. This in all probability is a rebound, not a retraction. The point of maximum impulse is carried out to or beyond the left mammary line. At the same time the area of cardiac dullness is widened (sometimes greatly) in both directions. It is not hard to realize in these signs a direct expression of that ventricular enlargement which is so characteristic of the rheumatic heart of childhood and adolescence.

(ii) At the apex a systolic bruit is present in the great majority of cases; it varies in loudness and length, but is always of the rushing and never of the rattling type, and is transmitted to the axilla. The louder and longer it is, the more likely it is to be accompanied by a systolic thrill. It is in position and time characteristic of mitral insufficiency. That in the production of such insufficiency a row of soft swellings, sometimes so small as to escape all but the most careful scrutiny, and never larger than mustard seed, can play any considerable part, is highly improbable, especially when we recollect that the mitral cusps are normally in apposition during systole over a large portion of their area. The cicatricial lesions of the valve in childhood are scarcely less trivial as a rule. No one who has seen autopsies on cases of rheumatic carditis and had opportunities of balancing for himself the importance of such lesions against an enlargement of the mitral ring which may admit so much as four whole fingers, can hesitate in deciding that such incompetence as existed must have been due to widening of the orifice by myocardial atony.

(iii) The other bruit which may be heard at the apex in the class of case under consideration is one heard during the second cardiac pause, following on the doubling of the second sound so common in such patients, and is at first barely audible. In larger hearts, however, it is sometimes so prolonged as to fill the whole interval between the end of the second sound and the beginning of the first sound. It may, in such cases, be accompanied by a gentle thrill; but it is not a crescendo murmur and it lacks the rattling character peculiar to the presystolic bruit of mitral stenosis. It is heard over a rather limited area above and internal to the point of maximum impulse, and varies in strength and duration even from day to day. With improvement under the influence of rest it is often shortened and may even disappear.

It was originally thought that this bruit showed the development of mitral stenosis; this theory was, however, set aside by Sturges (3) on the strength of post-mortem evidence, and others have been advanced since. Among these may be mentioned the 'valve-stiffening' and the 'auricular-systolic' hypotheses. I propose to advance a new explanation,[2] which is, I believe, the correct one. Every bruit implies a force propelling a current of blood and an orifice or obstruction modifying that current. The force is here supplied by ventricular diastole, for the beginning of the bruit coincides with the beginning of ventricular diastole, following as it does on the closure of the semilunar valves. A murmur similar in time and probably in origin is often heard in mitral stenosis, preceding, softer than, and separated from the typical presystolic murmur; and according to Mackenzie it persists even after the failure of auricular systole has destroyed the presystolic murmur. Here as in the Flint murmur of aortic incompetence and the diastolic murmur of adherent pericardium there is very great enlargement of the left ventricle, which will increase the force of the ventricular suction in diastole. Even in the normal heart the fall of intraventricular pressure occurring in the passage from systole into diastole is a very rapid one; and when the ventricular capacity is increased this fall will be more rapid still, for the same time-interval (or a shorter one) is occupied by a still larger drop in pressure. In the normal heart when $a$ = the diastolic capacity of the ventricle, and $b$ the systolic, the fall in pressure is expressed in terms of $a-b$. When, however, the ventricle wall is stretched in such a way that a portion of it is lengthened $c$ times by the stretching agent, the fall in pressure is expressed in terms of $ac^3-bc^3$; the fall in pressure is therefore greatly increased, and becomes a powerful force in the creation of a blood current from auricle to ventricle. In this way one factor in the production of an apical diastolic murmur is accounted for.

The other factor, the orifice or obstruction, is not so easy to imagine. At first it was supposed that the bruit indicated early mitral stenosis, and that the full development of such a lesion could be watched stage by stage. As already

[2] Dmitrenko's paper (*Rev. de méd.*, March, 1907) advances a somewhat similar theory; but I have not had an opportunity of reading the whole article.

stated, Sturges and others have found that this is not so. I have at least twice made a post-mortem examination on cases diagnosed as 'mitral stenosis' because this bruit was present, and found, instead of narrowing, an actual widening of the mitral orifice. Since then the bruit has been ascribed to stiffening of the valve-cusps. This, however, seems a little improbable; the amount of inflammatory exudation into the valve is, after all, small, and it is almost entirely confined (at any rate at first) to the marginal portions of the cusps. Fibrosis of the mitral cusps is rarely advanced before the age of sixteen is reached (Table III). Again, in many persons dying after the age of fifty sclerosis of the mitral segments is noted post mortem, and though it may amount to a considerable thickening of the valve at its edge it does not cause a murmur. Indeed, as Steell showed, in veritable stenosis there is often neither diastolic nor presystolic murmur. The disappearance of the bruit under the influence of rest is, like that of the systolic bruit already referred to, more likely to be due to a return towards the normal in the size of the ventricles than to any resolution of an inflammation the chief characteristic of which is fibroplasia. Another fact which points to a close relation between ventricular enlargement and the production of this murmur is the fact that in aortic incompetence and also in adherent pericardium, as well as in active rheumatic carditis, similar diastolic bruits are heard at the apex. In all these conditions the bruits are in time of origin ventricular-diastolic rather than auricular-systolic; in nature they are smooth and rushing rather than rattling; and they are as a rule diminuendo and not crescendo. Now, there is one alteration in the anatomy of the heart which is common to all these conditions, and that is dilatation of the left ventricle.

A very simple process of reasoning takes us a step further, and shows us that such dilatation increases the capacity of the ventricle more than it does the calibre of the auriculo-ventricular ring. First, suppose once more that the stretching coefficient is $c$: the calibre of the mitral ring is then multiplied by $c^2$, but the cubic content of the ventricle by $c^3$. And again, the calibre of the ring is probably not even multiplied by $c^2$, for the ring is mainly composed of comparatively unyielding fibrous tissue closed in for a fraction of its circumference by extensible muscle. It is therefore not unreasonable to imagine a ventricle whose capacity is increased out of proportion to the increase in size of the entrance to it; in other words, a relative stenosis is established, and the blood sucked through this relatively small mitral ring by the rapid expansion of an enlarged ventricle is thrown into vibrations which are appreciated by the clinical observer as a mid-diastolic murmur.

(iv) A sharp diastolic shock is felt at the inner end of the third left space, and a great accentuation of the pulmonic second sound heard at the same spot. Both of these are to be explained by two factors working concurrently: first, there is an increase of tension in the pulmonary circulation due to the insufficiency of the mitral valve, and secondly, the conus arteriosus dexter is brought into a closer contact with the thoracic wall (as autopsy shows) by the

general cardiac enlargement which thrusts the left lung aside and, so to speak, peels it off the anterior aspect of the heart.

(v) At the apex a curiously deliberate doubling of the second sound is often heard. This is probably due to delayed tension of the mitral cusps, as Lees has suggested; but since it may occur in the absence of much valvular thickening, it seems likely that such a delay may be in some way connected with the fact that myocardial changes are more pronounced in the wall of the left ventricle than in that of the right. To arrive at a fuller explanation of this interesting sign, clinical and pathological observations in a number of cases must be collected and correlated; for the moment it is enough to remark that its origin is conceivably connected with ventricular enlargement.

To summarize what has been said of these signs: in 75 % of my patients with rheumatic heart disease under sixteen years of age, the signs of disease were such as may entirely be accounted for by ventricular enlargement due to myocarditis. That such signs can be ascribed to disease of the cardiac muscle is, in my opinion, absolutely proved by autopsy, for all the signs detailed were present in two of the cases which fell to me for post-mortem examination, and in neither was there any but the slightest evidence of either endocarditis or pericarditis.

In the other 25 % there were signs indicative of pericarditis, mitral stenosis, aortic incompetence, or ulcerative endocarditis; in many instances (particularly in the pericarditic group) these special signs are merely added to, and do not replace, those already detailed. It is therefore true to say that the signs of rheumatic carditis in childhood are for the most part directly referable to disease of the cardiac muscle. It must not be forgotten, however, that every such case is a potential case of chronic valvular disease in later life, for though during childhood rheumatic endocarditis has on the whole little influence on the cardiac functions, yet it is almost invariably present in rheumatic carditis (in 90 % of my autopsy series), and the fibrosis which it starts is a progressive process, probably in the great majority of instances. There are cases in which a very definite carditis appears to get well: these recoveries are usually met with in my 'Group 1', and are therefore recoveries from myocardial disease, not from endocarditis.

The only remaining matter for discussion is the question of how far death in rheumatic carditis is directly due to myocardial disease.

(i) In a large number of such cases death is immediately preceded by acute dilatation of the heart: this was conclusively proved by Lees's (5, 6) observations.

(ii) What other lesions are there which are capable of causing death in rheumatic carditis? An examination of the autopsies already referred to gives results expressed in the following table:—

TABLE III.

| Lesions conceivably fatal in non-pyogenic carditis before 16 years. | Number of cases. | Percentage. |
|---|---|---|
| Pericardial adhesions (only those cases in which extrapericardial and intrapericardial adhesions existed, are included) | 16 | 18 |
| Pericardial effusion (4 to 10 ounces, with 4 cases of 'some fluid'), average of measured effusions = $4\frac{1}{2}$ ounces . . . | 8 | 9 |
| Aortic valvular sclerosis, including 'slight' degrees . . . | 12 | 13·5 |
| Mitral narrowing, including every case of definite constriction . | 6 | 6·75 |
| Ulcerative endocarditis. This includes several cases possibly not rheumatic, and therefore the percentage is unduly high . | 11 | 12·5 |
| Cases with none of the above lesions. In 7 of these, chorea, &c., probably contributed to the fatal issue . . . . . | 42 | 47·7 |

The apparent discrepancy in the figures is due to the occasional coincidence in one patient of two or more of the 'conceivably fatal' lesions.

A table compiled from post-mortem notes is not absolutely reliable, but in this instance the notes were almost uniformly thorough; consequently the table may be taken seriously in its statement that nearly half the cases died without any adequate valvular or pericardial cause. This is the more significant because under 'pericardial effusion' several quite small quantities were included, which in a previous paper were ignored as being not enough to cause death.

(iii) Poynton (20) has shown, in a study of 100 fatal cases of rheumatic carditis, that there was undoubted evidence of fresh cardiac infection in 86. My own figures are in close agreement; recent carditis was present in 75 out of 88 cases, or in 85 %.

(iv) My work, as well as that of others, shows that recent myocardial changes are practically always present in acute rheumatic carditis.

Probably, then, death in rheumatic heart disease occurring before the age of sixteen is reached is more often due to acute inflammation of the myocardium than to anything else. Even in cases above this age, with valvular sclerosis and pericardial adhesion, myocarditis may play an important part, as the following very significant case shows:

A youth of twenty-one, who was known to have suffered from aortic incompetence, the result of previous rheumatic attacks, was admitted to the Bristol General Hospital under my colleague, Dr. George Parker (who kindly allows me the use of the notes), with indefinite malaise and pains, a little fever, and signs of compensated aortic disease. A few days after admission he died quite suddenly in a syncopal attack. The autopsy (performed by myself) showed a large heart with an obliterated pericardial sac, fibrosis of the aortic and mitral valves, and an ulcer of one of the mitral cusps, so small that it was

almost overlooked in spite of a careful search. The muscle, under the microscope, showed areas of fatty change, and, what was even more conclusive, several of the nodules described at length in this paper. Here, I consider, is absolute proof of a muscular re-invasion by the rheumatic virus with fatal results. This is the only case of the kind fully examined so far by me; but that many cases of chronic valvular disease dying in adolescence and early adult life exhibit after death evidences of fresh inflammation is proved by a table based on recent post-mortem records at the Bristol General Hospital. 121 cases exhibiting chronic valvular disease are here tabulated according to the age at which they died. Many of those who came into the later decades were, of course, merely cases of that calcareous degeneration of the valves which commonly accompanies aortic and coronary atheroma; but it is safe to suppose that the great majority of the patients dying before fifty were suffering from the permanent results of a rheumatic carditis. How far the acute terminal changes were also rheumatic is difficult to judge, but in many instances the acute endocardial and pericardial lesions were such as we are used to see in acute rheumatic carditis. The ages begin at seventeen, because I have already said that of the patients dying of acquired non-purulent heart disease at or under sixteen, 85% showed evidence of acute inflammation. In the decade 17–26, I have included as evidence of acute carditis great dilatation of the ventricles associated with a very moderate mitral fibrosis; this was described in two cases.

TABLE IV.

| Age at which death occurred. | Cases of chronic valvular disease in each decade. | Cases with acute cardiac inflammation in each decade. | Percentage of chronic cases showing acute changes. |
|---|---|---|---|
| 17 to 26 | 18 | 13 | 72·2 |
| 27 to 36 | 16 | 7 | 43·7 |
| 37 to 46 | 34 | 6 | 17·6 |
| 47 to 56 | 26 | 4 | 15·3 |
| 57 to 66 | 16 | 2 | 12·5 |
| over 66 | 11 | 0 | 0 |
| all ages together | 121 | 32 | 26·4 |

The striking fact brought out by this table is the great liability of those who suffer from chronic valvular disease to incur fresh cardiac infection in earlier adult life as well as in adolescence. In many of the cases included in the first two decades such outward and visible changes as were present, whether acute or chronic, were quite inadequate to cause death. The same might have been said of the case detailed above, which is therefore but one of a group. The

reason why death occurred was supplied by examination of the cardiac muscle in that one case, and in all probability many of the deaths tabulated as occurring between seventeen and thirty-six are susceptible of a similar explanation, viz: that a fresh attack of rheumatic carditis brought about a fatal disturbance of compensation by its direct effect upon the ventricular muscle. These observations, of course, require further examination of cardiac muscle from suitable cases before they emerge from the realm of hypothesis, but they are at least highly suggestive.

## Summary and Conclusions.

### *Macroscopic Myocardial Changes.*

1. Dilatation of both ventricles is constant, and often of considerable degree. The auriculo-ventricular orifices share in the stretching.

2. Hypertrophy of both ventricles is usually present, and in many instances without any obvious mechanical cause.

3. The naked-eye appearance of the cardiac muscle is but little altered as a rule.

### *Histological Changes.*

1. The parenchymatous cells are the seat of a fatty change, which is most pronounced in the wall of the left ventricle, particularly in the papillary muscles and beneath the pericardium. No other important change has been constantly noted in the cells themselves.

2. In the stroma nodules are formed consisting entirely of large cells, many of which are multinucleate, and which seem to be fibroblastic in nature. In the formation of these nodules other cells play quite a subordinate part. They develop especially in the neighbourhood of arteries and arterioles; the left ventricle is far more affected than the right, particularly near the root of the aorta and the mitral ring, and at the apex near the interventricular septum. Few nodules are found in the septum itself, and the same applies to the papillary muscles.

3. Foci of leucocytosis, chiefly polymorphonuclear, are also seen. These are pericapillary, and are found especially in the papillary muscles.

4. Various arterial inflammations occur, especially a nodular periarteritis. Aortitis is generally present.

5. In hearts which have passed through a stage of active carditis certain cicatricial lesions of the myocardium remain to mark the sites of previous nodules.

### *Interpretation of the above changes.*

1. The nodules are inflammatory and probably represent a reaction of the connective tissues at the actual points of infection. They appear to be characteristic of rheumatic as opposed to other forms of carditis, and changes

histologically similar are seen in rheumatic endocarditis and pericarditis and subcutaneous rheumatic nodes. Their close relation to the arteries is a further proof of the fact that in rheumatic carditis the heart is invaded by the coronary avenues.

2. The areas of leucocytosis represent oedema due to passive venous congestion.

3. Toxaemia accounts for, no doubt, the greater part of the fatty metamorphosis; but it must be remembered that a similar change occurs as the result of chronic venous congestion and of hypertrophy, both of which are seen in most cases of rheumatic carditis.

4. Ventricular dilatation is to be ascribed to muscular atony under the influence of toxaemia. It is greater in degree than the histological changes would lead one to expect.

5. The hypertrophy of the ventricles, occurring as it does sometimes without obvious cause, may also be referable to the 'direct' action of some toxin. There is some evidence to support the view that the poison produces this effect by inducing myocardial over-action.

6. The myocardial lesions occurring in rheumatic carditis are of so special a kind as to lend definite support to the conception of a specific rheumatic infection.

*The influence of the foregoing lesions on the cardiac functions.*

1. The physical signs characterizing the rheumatic heart disease of childhood are in a majority of cases referable to the myocardial lesions, and not to those of the serous layers. This is substantiated by post-mortem evidence.

2. Death during childhood from rheumatic carditis is, more often than not, directly due to myocarditis.

3. Some, at any rate, of the deaths occurring in rheumatic heart disease during adolescence and early adult life are probably caused by the muscular lesions.

I have, in conclusion, to express my sincere thanks to those of my colleagues who have allowed me to use material; to Dr. Walker Hall, Professor of Pathology, University College, Bristol, and to Dr. E. V. Dunkley, Pathologist to the Bristol General Hospital, for much kind assistance and advice. For the microphotographs I am indebted to the kindness and skill of my friend Dr. Newman Neild.

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## DESCRIPTIONS OF FIGURES.

PLATE 5, FIG. 1. A 'submiliary nodule' lying in the connective tissue between muscular bundles (wall of left ventricle).

FIG. 2. The same nodule, more highly modified; in the centre several multinucleate cells are seen.

PLATE 6, FIG. 3. An arteriole from the wall of the ventricle surrounded by a nodule whose cells are arranged in concentric layers.

FIG. 1

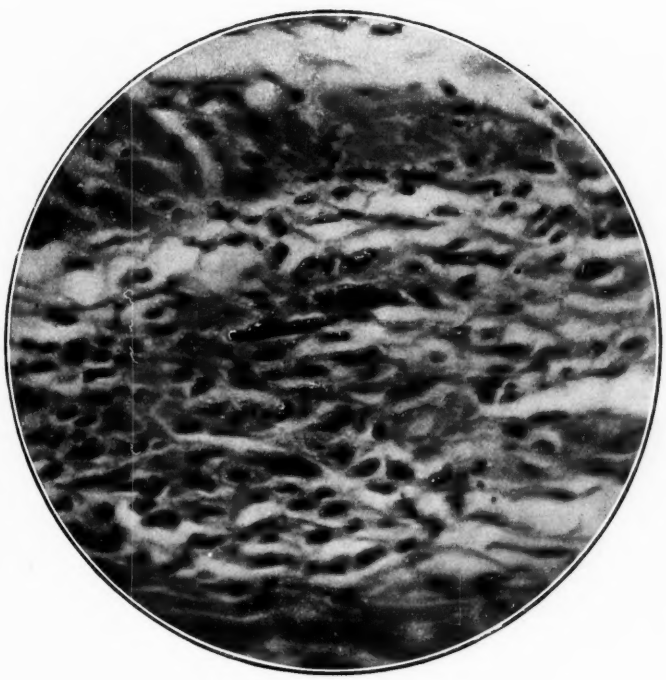

FIG. 2

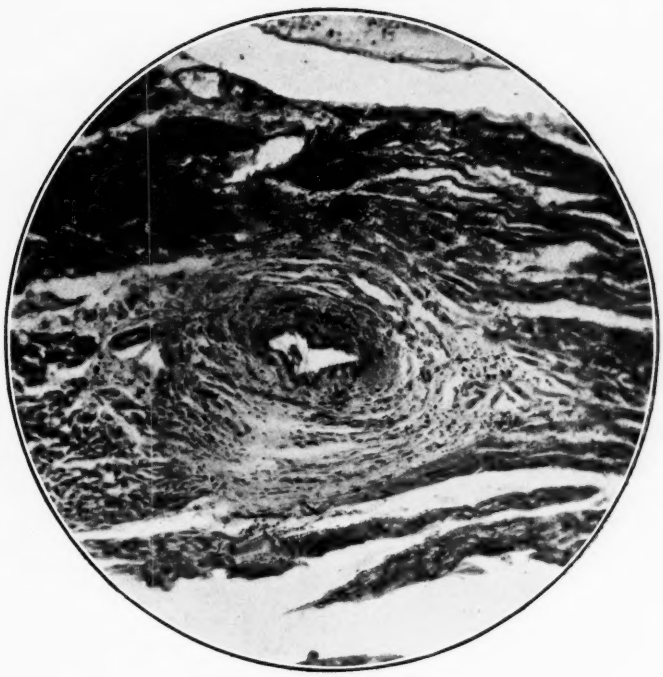

FIG. 3

# MONGOLISM AND ITS PATHOLOGY: AN ANALYSIS OF EIGHT CASES

By W. BERTRAM HILL

With Plates 7, 8

Dr. Langdon Down, in the year 1866, in an article published by him in the London Hospital Reports of that year, was the first to point out that certain classes of feeble-minded children might be referred to definite ethnological families. He described cases presenting the typical physiognomy of the Negroid family: of the Malay variety and of the North American type; and lastly that variety of genetous idiocy which presented the Kalmuc or Tartar type of features, with flat broad faces, oblique palpebral fissures, short noses with a broad depressed bridge, short sparse brownish black hair and small rounded head much deficient posteriorly, which has ever since been spoken of as 'Mongolian idiocy'. Although Dr. Down's classification of mental enfeeblement in children has now been definitely abandoned, the term 'Mongol' still survives and is an expressive and descriptive one.

*Aetiology.* The most striking and constant feature in the aetiology of Mongolism is the presence of some depressing influence during the gestation period of the mother, in conjunction with the fact that fully 50% of Mongolian idiots are late members of a large family and born after the mother has reached the age of 40 years. In my own series of eight cases there was a definite history of bad health in the mother during her pregnancy in four, and in two of these four the mother spontaneously gave an account of a fright whilst carrying the child. The following table shows the ages of the parents at the date of the birth, and the position of the children in the family:—

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Case No. | 1, | father's age | 44, | mother's age | 41: | third and last child. |
| „ | „ | 2, | „ | „ | 41, | „ | „ | 41: tenth and last but one. |
| „ | „ | 3, | „ | „ | 43, | „ | „ | 39: eighth and last. |
| „ | „ | 4, | „ | „ | 43, | „ | „ | 43: tenth and last but one. |
| „ | „ | 5, | „ | „ | 27, | „ | „ | 24: second and last. |
| „ | „ | 6, | „ | „ | 42, | „ | „ | 41: ninth and last. |
| „ | „ | 7, | „ | „ | 42, | „ | „ | 40: twelfth and last but one. |
| „ | „ | 8, | „ | „ | 52, | „ | „ | 40: first and last. |

Weygandt, in a study of 37 cases, states that 'in the majority of cases the patients were last children of a large family, and that the parents were often old, with disparity in their years'. And Zubizanetta, Mitchell and Bourneville have found similar histories. Bourneville has thought, in view of the fact that he found the thyroid gland abnormal in two cases, that the condition might be due to defective function of that gland. But thyroid treatment has not borne out this hypothesis.

*Incidence.* Mongolism forms roughly speaking from 3 % to 4 % of all classes of feeble-minded children in English asylums. From published statistics it appears to be rather less common on the Continent, though this is probably due to the fact that until recent years these cases were much confused with infantile myxoedema. No country appears to be exempt from the condition, and it is fairly common in all large out-patient clinics. It is at least four times as frequent as cretinism. Of my eight cases, three were males and five females; and of 180 cases collected from all sources 46·5 % were females and 53·5 % males.

Mongolism may be defined as a condition of antenatally-arrested development, both physical and mental, characterized by brachycephaly, combined with the type of physiognomy seen in the Mongolian races, together with, in the later years, a definite and characteristic appearance of the tongue.

## *Physical Characteristics.*

*The Head.* All authors are equally agreed that one of the most constant and distinguishing features of Mongolism is marked brachycephaly, or a shortening of the antero-posterior diameter of the skull. In one instance only, in the whole of the literature upon the subject, have I come across an account of a case in which brachycephaly was said to have been absent, and in this instance the other characteristic features of the condition were said to have been only slightly marked.

Viewed as a whole the skull is distinctly round and there is usually marked flattening of the occipital region and absence of an occipital protuberance; the plane of the occiput tends to be parallel with the plane of the face and forehead; and the antero-posterior and transverse diameters of the skull are nearly equal. The following are the measurements in my own cases:—

| | | | | |
|---|---|---|---|---|
| Case 2, | breadth | 11 in., | length | 11½ in. |
| „ 3, | „ | 10½ in., | „ | 10 in. |
| „ 4, | „ | 10½ in., | „ | 11 in. |
| „ 5, | „ | 9½ in., | „ | 10 in. |
| „ 6, | „ | 8¾ in., | „ | 9½ in. |
| „ 8, | „ | 10½ in., | „ | 11½ in. |

The fronto-occipital circumference is also greatly diminished, and this is shown in the accompanying table:—

| | | |
|---|---|---|
| Case 1, age | 1½ yrs. | 17 in. |
| „ 2, „ | 5½ yrs. | 18¼ in. |
| „ 3, „ | 3 yrs. | 17 in. |
| „ 4, „ | 8 yrs. | 18 in. |
| „ 5, „ | 11/12 yr. | 16 in. |
| „ 6, „ | 8/12 yr. | 14½ in. |
| „ 8, „ | 4 yrs. | 18½ in. |

The fontanelles and cranial sutures remain open much later than is normally the case. The average age at which the fontanelles were closed in Muir's series of 26 cases was 2·5 years—the latest being 4 years; and in several instances the posterior fontanelle was patent at the fourth, fifth, and even the tenth month. Still reports a case in which the anterior fontanelle was open at 4¾ years. In one of my own cases the posterior fontanelle was patent at the eighth month, and in other two cases the anterior fontanelle was wide open at the eighteenth month and the fourth year.

Of the hair, Langdon Down says in his original description of the condition, 'They rarely have black hair as in the real Mongol, but it is of a brownish-black colour, straight and sparse.' Of my cases, one had long fair hair, one very dark brown, and the remainder light brown. In all of them it was fine in texture and abundant, and in no case could it be described as 'straight and sparse'.

There is no constant anomaly in the shape of the ears which can be said to be at all characteristic of the condition.

The face is decidedly the most characteristic feature of Mongolian idiocy. It is round, often depressed as a whole, when the lower part of the forehead is on a plane posterior to that of the upper. The length and breadth are nearly equal, and the cheeks are chubby and of a ruddy colour which extends from the malar bones to the chin. The following are the measurements of the face in four of my cases:—

| | | |
|---|---|---|
| Case 2, breadth | 4 in., | length 4¼ in. |
| „ 3, „ | 4¼ in. | „ 4¼ in. |
| „ 4, „ | 4¼ in. | „ 4¾ in. |
| „ 6, „ | 4 in. | „ 4½ in. |

The forehead is generally well shaped, and the face in profile (see Fig. 3) is as fully distinctive of the condition as the full face (see Figs. 1, 2). The nose is short, with a broad depressed bridge, and the cartilaginous portion is often rather broad. Bourneville states, however, that it is common to see cases with straight aquiline noses.

The eyebrows tend to run upwards and slightly outwards. The palpebral fissures are narrow and slope downwards and inwards. Fennel reports one case in which the direction of the fissures was reversed and three cases in which their direction was normal. In the earlier years there is frequently present strabismus



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or nystagmus, more commonly the former, occasionally both. Muir in 26 cases had five with nystagmus and seven with convergent strabismus. Of my own cases, three only showed this condition, as follows :—

Case 1, strabismus at one year, absent at 18 months.
Case 2, convergent strabismus at three years, absent at five years.
Case 3, lateral nystagmus and convergent strabismus at the third year.

Epicanthus is frequently present, though by no means always. When present, however, the features are much more Mongolian in character than those without it. It was present in five of my eight cases. Weygandt, in an account of 37 cases, says, ' Epicanthus is frequent.'

The mouth is small, round, and constantly open ; but continuous salivation is absent. The lips are somewhat everted, especially the lower one, which is usually thicker than normal. A feature by which I was particularly struck, in my own series, was a transverse furrowing of the mucous membrane of the lower lip, which reminded me very much of the similar condition of the tongue which is so constant a feature of older Mongols. It was marked in five of the cases and slightly so in two.

In younger subjects the tongue is nearly always protruded, and this protrusion does not necessarily disappear with age. Vogt reports a case, 16 years of age, in which the tongue was constantly protruded. The most striking condition of the tongue does not seem to appear till some little time after birth. The papillae become enlarged and the surface of the organ covered with numerous and deep fissures. The term ' hacked ', which has been used in this connexion, describes the condition exactly. At the Lancaster Asylum, where through the kindness of Dr. A. Douglas I saw a large number of Mongols, so marked was the fissuring of the tongue, that it would have been possible to diagnose the condition of the patients by that aid alone. In my own cases, enlargement of the papillae occurred as follows :—

| | | |
|---|---|---|
| Case 1, | age $1\frac{1}{2}$ yrs. | Papillae enlarged : slight fissuring. |
| „ 2, | „ $5\frac{1}{2}$ yrs. | Papillae enlarged : no fissuring. |
| „ 3, | „ 3 yrs. | Normal. |
| „ 4, | „ 8 yrs. | Papillae slightly enlarged : slight fissuring. |
| „ 5, | „ $\frac{11}{12}$ yr. | Normal. |
| „ 6, | „ $\frac{8}{12}$ yr. | Normal. |
| „ 8, | „ 4 yrs. | Papillae much enlarged : dorsum covered with numerous fissures. |

Deformities of the hard palate are common, the chief variety being the V-shaped. I found it present in six of my cases, and in one the palate was higher than the normal. Muir found palatal deformities in 67 % of his cases.

Dentition is much delayed and frequently very irregular. The second dentition is not so irregular and often occurs at the proper time. Vogt says

there is irregularity in the order of eruption of the milk-teeth in from 34% to 80% of the cases. Dentition in my own series occurred as follows:—

Case 1, 18 months. First tooth cut at 14th month; a molar.
" 2, 5½ yrs. " " " " 3rd year; the right upper second molar.
" 3, 3 yrs. " " " " 2½ yrs.; lower central incisors.
" 4, 8 yrs. " " " " 4th year.
" 5, $\frac{11}{12}$ yr. No teeth.
" 6, $\frac{8}{12}$ yr. No teeth.
" 8, 4 yrs. First tooth cut at end of 1st year.

*The Trunk.* The chest is well formed and presents nothing at all abnormal or characteristic of the condition. There is frequently a certain amount of bronchitis present, and in a proportion of cases signs of congenital morbus cordis. In what proportion of cases of Mongolism congenital heart disease exists is very difficult to estimate indeed. It is said to be more common in Mongolism than in any other variety of idiocy. Garrod and others have stated that it is very rare to find evidence of heart malformation in cases surviving 3 years of age. Fennel, however, has seen three cases, aged 9, 13, and 27 years, in which there was evidence of congenital heart disease. In my own series, ranging from 8 months to 8 years, there was no such evidence. In 188 cases, collected from various sources, evidence of heart disease was found in 13·3%.

Spinal curvatures are rare, and when present are due to muscular weakness. Late development of the normal spinal curves is frequent. In one of my own cases, aged 3 years, which was unable to walk, the normal curves had not developed. Ossification is much delayed, and this is seen in the accompanying radiograph of the hand of one of my cases, aged 8 years (see Fig. 7). The hands are short, broad and stumpy; the fingers round, thick, and tapering towards their extremities, and the thumb and little finger are shorter in proportion to the other fingers than normal. In a proportion of cases anatomical anomalies are present in the phalanges; but these are not more frequent than in other forms of idiocy. The Mongolian hand does not always conform to the above description; it may in every way be quite normal; this occurred in two of my series. The feet are more frequently normal than the hands, though they may be short, thick and clumsy.

Laxity of the joints is a marked feature and a greater range of movement than is normal is often obtainable. Whether this is due to the laxity of the ligaments surrounding the joints or to deficient tonicity of the muscles, has not been determined; but in all probability it is due to the latter. It was possible in one of my own cases to bend the fingers backwards almost on to the dorsum of the hand, without causing the child any pain, and to abduct the thigh to a right angle with the body.

*The Extremities.* The limbs are well formed, and as a rule, along with the remainder of the body, well nourished; but the muscular strength is deficient. Sutherland and Vogt state that the long bones and extremities are as a rule

shorter and smaller than normal. With these exceptions I do not know of any other observer who has described anything abnormal with regard to the limbs. Certainly in my own series the extremities were of normal size and development.

*Physical Development.* At birth these cases are extremely weak and undersized, and their growth proceeds very slowly. There can be no doubt whatever that large numbers of these children die without their true condition ever having been diagnosed. Later on, if they survive, they come to look well nourished and fat, especially about puberty, but their powers of resistance to cold and various infections is much below the normal. The body temperature is frequently below the normal, though not invariably so. It was subnormal in four of my cases. Constipation is frequent, though not obstinate. Mucous diarrhoea (Eustace Smith) is said to be very common. The skin has usually been described as rough, dry and papillated. Muir, however, says that, with the exception of one case, the members of his series all presented a smooth white skin; and my own experience coincides with Muir's. In spite of the rosy cheeks of these children, there is a moderate degree of anaemia of a simple type. The red cells are diminished, as is also the percentage of haemoglobin. I made a complete clinical examination of the blood in all my cases; the lowest percentage of haemoglobin amounted to 70 %, and the lowest red cells count to 3,600,000. No pathological alteration was found on making a differential leucocyte count.

As a class they are undersized, though the degree of dwarfism is not in any way characteristic as it is in cretinism. Kassowitz states that on the average they are from 5 to 10 cm. below the average height. Out of eleven cases reported by Bourneville six were 10 cm. less than the normal, and five were 10 cm. above the average height. In my own series of eight cases the average diminution in height was 4·5 in.

Puberty is reached late and the pubic and axillary hair is usually ill developed. All varieties of malformations of the external genitalia have been seen in the male. In the female, menstruation does not occur till late, soon ceases, and is very irregular. Vogt says these cases are always sterile. The breasts are small and ill-developed in all cases.

*Mental Characteristics.* Mongols display all grades of mental deficiency, ranging from the mildest forms of imbecility to complete idiocy, the commonest form being imbecility. During infant life their disposition is one of apathy, and in most cases the mothers will say that the child is exceedingly good and easy of management. Later on they become lively and restless individuals. They are extremely good tempered, cheerful, affectionate, and easily amused; very playful and even original when unobserved. As a rule, they are very observant and will often mimic muscular actions. Shuttleworth says, 'Their powers of mimicry are often extraordinary; their love of music great; their idea of time as well as of tune remarkable; so that they are apt at drill and dancing.'

In marked contrast to the generality of feeble-minded children, they are never erotic nor do they practise onanism.

The development of speech is much delayed, and it is quite common for a child of 4 or 5 years old to be unable to give utterance to a single syllable; though the order in which speech develops is the same as that of normal children. One of my cases at 8 years old could only say 'dada' and 'mama', and these words rarely. A case is reported of a female Mongol (aged 40) who was quite unable to speak at all (Fraser).

*Motor System.* More striking perhaps than the delayed acquirement of the powers of speech is the late development of the power of walking and of movement generally. These cases are late in holding up the head and in sitting up. Kassowitz states that they do not often hold up the head till the third year. In two of my cases, aged 8 and 12 months, neither could hold up the head or sit up; and 3 cases, aged $3\frac{1}{2}$ and 7 years, had made no attempt to walk.

*Nervous System.* The sight and hearing are good. The sense of taste is said by some observers to be dulled. There are no muscular tremors and cutaneous sensibility is much diminished. With regard to the various reflexes, opinions differ. Vogt says the knee-jerk and plantar reflex are somewhat increased. Fennel gives the following results in twenty cases: brisk in nine, normal in six, absent in five. In my own series, the knee-jerk was absent in six cases and only a sluggish response obtained in one, and the plantar reflex was extensor in character in the whole series. Foot and patellar clonus were never obtainable.

### *Morbid Anatomy and Pathology.*

One of the most striking features of Mongolism is the close resemblance the cases have to each other. There is no other variety of idiocy, congenital or acquired, in which such resemblance is seen. The same facial characteristics are present in each case, and much the same mental features. This is well illustrated by a statement in an article on the subject by Weygandt, who says, 'The outward resemblance of these children is so great that parents visiting an asylum can with difficulty recognize their own children.' Such being the case, it is reasonable to suppose that there must be some common cause accountable for the condition. Pathologists, however, have not yet succeeded in tracing its origin to any one organ, as in cretinism; and sufficient post-mortem work has not yet been performed to enable any one to say with any degree of certainty what the cause of the condition really is.

Most observers are agreed, I think, that the cause of the disease is to be looked for either in the cranium or in its contents. Bourneville is the only observer, whose work I have been able to study, who has been led seriously to think that the cause of the disease might be situated in some other organ of the body; and the only organ other than the brain in which he found distinct pathological changes was the thyroid gland; and this in two cases only.

There would appear to be two schools of thought regarding the origin of the disease.

1. First, those who consider that the causation is to be sought for either in the antero-posterior shortening at the base of the skull, or in the relative diminution in size of the structures at the base of the brain. The principal factor in support of this hypothesis is the presence of antero-posterior shortening at the cranial base. This shortening may depend upon one of two conditions—either that there is a premature ossification of the bones forming the base of the cranium, or that there is a cessation of growth of the structures at the base of the brain, in consequence of which there is no need of further expansion of the basis cranii, so that the bones ossify earlier than would otherwise be the case. At first sight this explanation would appear to be reasonable, and the support which it has received probably arises from the fact that it follows more or less the line of reasoning primarily advanced to account for cases of microcephaly, viz. that in these cases there is a premature ossification of the bones constituting the vault of the skull, and in consequence an imperfect development of the cerebral lobes; but this explanation has been definitely relinquished by those observers who have paid most attention to the condition, and it is now considered that its origin must be sought for in the brain itself. In Mongolism, however, some evidence has been adduced in support of the hypothesis that the cause should be looked for at the base of the brain.

Wilmarth, in the study of the brains of five Kalmuc idiots, says: 'In all these the brains were of good size for imbecile brains, the pons and medulla alone being very small, and weighing in each case about half an ounce, the normal weight being about twice as much. The condition may be due to the absence of certain cell groups in this region.'

Sutherland, in an account of the post-mortem examination of a Mongolian idiot, aged 14 days, says, 'The pons and medulla were strikingly small relative to the size of the cerebral hemispheres.' Bourneville has described these as being normal, and no other observers that I am aware of have furnished any evidence of the diminution in size of the structures at the base of the brain.

Of the premature ossification of the bones entering into the formation of the base of the skull I have found no evidence. On the contrary, in the reports of the post-mortem examinations which I have been able to collect from the literature, the basal bones are said to have been normal.

Leonard Guthrie, at the post-mortem examination of an adult Mongol, demonstrated that the cranial bones were quite normal. Fraser reported that in the skull of a Mongol aged 40 years the basal bones were normal. He says: 'Most of the sutures were wide open and the metopic suture persistent throughout its whole extent. There were five Wormian bones in each lambdoidal and squamous suture. A wide interval exists between the petrous bone and the basilar portion of the occipital. In these spaces Wormian bones of poor cancellous tissue are to be found. The spheno-basilar synchondrosis is not visible, nor any ridge or elevation to mark its site. The sutures between the lesser wings of the sphenoid and the frontal bone are wide open. From the condition of the sutures the skull could have expanded in all directions.'

2. The second school, consisting of observers who have paid most attention to the structure of the cortex of the brain, consider that they have found there sufficient pathological evidence to justify them in assigning the causation of the disease to that area of the brain.

Of the various observers who have made detailed examinations of the brain, both macroscopically and microscopically, the only account of a detailed examination of the cortex of the brain of a Mongolian idiot which I have been able to find in the English literature is one by Fraser, who says :—

'The membranes were normal. The weight of the brain was small; weight 49 oz. The configuration was asymmetrical. There is bulging in the right frontal and left parietal regions, and slight flattening in the left frontal and right parietal lobes. The convolutions are slightly flattened. The course of the gyri is simple, but the principal fissures are well marked. The sulci vary in depth. Each parieto-occipital fissure on the left side runs outward for nearly two inches. The posterior part of the third temporal convolution is very narrow (it is of interest to mention here that the patient could not speak). The island of Reil on both sides is small. The superior gyrus of both temporo-sphenoidal lobes is very narrow. *The Base.*—The nerves, medulla and crura showed nothing abnormal. *Microscopically.*—Grey matter 4–5 mm. thick anteriorly, 3–4 mm. thick posteriorly. The ventricles are normal. The grey matter showed the average number of tripolar and multipolar cells of normal size and definition. The nuclei of the neuroglia were not increased; no abnormal fibrillation. The perivascular canals were dilated. The hyaline membrane was puckered and thickened. *The Cerebellum.*—Left lobe slightly longer in the transverse diameter than the right.'

Shuttleworth, in writing on the condition, states: 'The brain is not necessarily small, but is characterized by great simplicity of development and paucity of multipolar cells. The convolutions are large and coarse, and there are no secondary convolutions.'

Of the Continental observers, Bourneville, in collaboration with his pupils Philipp and Oberthur, has done the most original and elaborate work upon the morbid histology of the Mongol brain. The following is his account of an examination of the brain, taken from his *Recherches sur l'épilepsie et l'idiotie*:—

'The vessels and nerves at the base of the brain are all symmetrical; the convolutions are generally weak, especially those of the frontal region; the sulci very shallow and the ventricles normal. The corpus callosum is also thick. The bulb appears normal.

'All the lesions are essentially diffuse, and involve the white as well as the grey matter and the meninges. They are more pronounced at the level of the frontal cortex, at the back of the parietal region near the calcarine fissure, and at the occipital region. The soft meninges are slightly thickened

and more opaque than normal. Microscopically they are rich in vessels, their connexion with the subjacent nerve tissue is weak on the dome of the convolution as well as in the interior of the sulci; after decortication there is no erosion of the grey substance. The histological examination shows that it is a fibrous meningitis, sending into the subarachnoid region numerous lengthenings and fine vessels. There are no clumps of lymphocytes to be found around the vessels, nor the layer of embryonic cells so customary in certain types of infantile meningo-encephalitis. With regard to the vessels of the meninges, there is no endarteritis, no endophlebitis, but there is a thickening of the external coats, presenting occasionally a hyaline appearance. A true inflammatory condition is seen nowhere.

'The cortex, macroscopically, is thinner than normal, and this thinning extends to the white substance; there is thus a true microgyria without any central sclerosis.

'In addition to thinning of the strata of the grey matter, there is marked rarefaction of the cells. The cells are small, almost of equal size in all the regions, often rounded, occasionally fusiform, giving the appearance of neuroblasts. The nucleolus is well marked and easily made out. There is no pigmentary overloading of the cells, and their disposition is fairly regular. The fibres of the Exner net, although it has nowhere disappeared, are very thin, and this thinness is characteristic. The other strata of tangential fibres, both subcortical and intracortical, are not so well represented. The bundles of the radial fibres are also equally scarce, and the direction in many places very irregular. The neuroglia is hardly visible, and nowhere are spider cells with their processes to be found. Vessels are numerous in the last layer of the cortex only, and they present the same appearance as those found in the white substance. The convolutions penetrate much less than normally, but this was to be expected after the scarcity of the radial fibres described above. Individually these fibres are extremely thin. Between these fibres the fibrillary neuroglia is scarce. There is no appearance of sclerosis. Abundance of vessels characterizes the white substance; their sheaths are distinctly hyaline in appearance. More noticeable than the number of the vessels is the increase in thickness of the tunica adventitia.'

No complete account of the examination of the brain in Mongolism appears to exist in German literature, and the investigations of German pathologists seem to have been confined almost solely to the macroscopical appearances of the organ.

Thiemich and Wernicke furnish an account of the macroscopical appearance of a brain of a Mongol 5½ years of age. They state:—

'The weight was 1,045 gms. The convolutions were thick, and there was an atypical appearance of the operculum and the island, which latter was in places only covered by the soft membranes. After removing the pia it was seen that the part which appeared to be uncovered was really the narrowed

part of the first temporal convolution which had been pushed below the surface. On the left hemisphere, below the surface, was seen a part of the third frontal convolution which hides between the projecting portion of the third frontal convolution, and which corresponds to a normal Broca's gyrus. The frontal gyri in their posterior parts, with the exception of the lowest, were separated from the anterior central convolution by a deep transverse fissure, which corresponded in direction with the central fissure, but was not closed at its termination. On the right hemisphere Thiemich found similar but rather less marked changes, whilst in section of the frontal region he could find no abnormalities. No microscopical examination was undertaken.'

Fromm reports, after the examination of the brain of a patient aged 1½ years, that with the exception of a marked flattening of the convolutions, there was no departure from the normal. He undertook no microscopical examination. Epstein, after making a microscopical examination of the brains of several Mongols, found nothing abnormal. Heubner reports a case he saw, and says, 'there was only to be found defective development of the frontal lobes.'

From the foregoing accounts of the post-mortem examinations of the various observers, it is clear that there is little or no evidence that the cause of Mongolism is situated either in the structures at the base of the brain or in a premature ossification of the basal bones of the skull. On the other hand, there is ample evidence of pathological changes in the cerebral cortex, and these changes do not appear to be of an acute inflammatory nature, but strongly suggest the presence of a toxic degeneration or chronic inflammation; this may be brought about by some mild infection in utero, the origin of which at present is unknown. The maximum lesion appears to be situated in the fibre rather than in the cellular strata.

### *The condition of the ductless glands.*

Having in mind the successful results obtained in cases of sporadic cretinism by the administration of the extract of the thyroid gland, some observers have examined the ductless glands in cases of Mongolian idiocy, in the hope that some pathological evidence would be found which would justify them in treating these cases with the active principle of any one, or a combination of them. As I have stated before, Bourneville is the only observer who has found any pathological changes in the thyroid gland; and the following is an account of his observations. Of the first case he says:—

'At first sight the gland looks normal. The vesicles also appear normal. The larger and medium vesicles are much reduced in number, and the lobules are much less stretched out. The trabeculae are much hypertrophied and the vessels sclerosed. Here and there are interstitial haemorrhages, a little pigment, and some fatty infiltration. The capsule is uniformly much thickened. There are modifications of the thyroid tissue, which, though slight, show its state to be pathological.'

In the second case: 'The thyroid gland shows great alterations in all its

elements. In all the vesicles the colloid material is almost completely replaced by cells derived from glandular epithelium. The vesicles are completely choked with these cells. The trabeculae are thickened and infiltrated with young connective tissue. Here and there are numerous vesicles filled with fat. The capsule is very thick. In short, there is extensive thyroid sclerosis.'

With the exception of these two cases quoted above, Bourneville states that he has, in every other instance in which he has examined the thyroid gland in Mongolism, found it to be structurally healthy.

Thiemich and Chartier report that on examination they have found the thyroid normal. Fromm reports a case in which, he says:—

'The gland was of insufficient development for the child's age. There was a definite hypoplasia of the gland. Agreeing with this macroscopical appearance of the gland there was found to be microscopically an imperfect development of the glandular substance and a deficiency in the colloid substance as compared with the abundant connective tissue.'

With regard to the condition of the supra-renal bodies in Mongolism, one report only is to be found in the literature, and this is furnished by Paul Lang, who says:—

'These (the supra-renals) showed changes due to necrosis. There was atrophy of the cell bodies, and granular degeneration of the protoplasm. The cells were imperfectly separated from one another, and the protoplasm showed diminished receptivity of the stain.'

Sutherland states that he has found the supra-renals, the thymus and the thyroid glands normal in cases of Mongolism. Lang makes a similar statement with regard to the thymus.

*The condition of the bones and cartilage.*

Curiously enough, two observers only (and both of them German) have thought to make an examination of the bone and cartilage in cases of Kalmuc idiocy, and in both these cases the examination seems to have been carried out with the view of ascertaining whether there were any changes in the ossification which could be attributed to rickets, or in any way allied to rickets. Nunheim appears to have been the first observer to make any definite statement with regard to this, and he says 'there is a normal ossification in these cases'. Kassowitz and Epstein hold the same view, and the latter states that there are no rachitic changes in the bone. Kassowitz and Lang are the only observers to give a full description of any such examination, and the former reports as follows:—

'The proliferation of the cartilage cells in the zone of the enlarged cells placed in rows is very markedly increased, so that the breadth of the proliferation zone exceeds the breadth of cell columns. The latter corresponds in its dimensions with the normal, but does not show the usual regular order of the cell columns; and the layers of hyaline ground substance between the columns were narrower and less regular than usual. Also the projecting marrow spaces from within the cell columns do not show the normal relations, the marrow spaces not

being finger-like processes, but in the form of rounded knob-like projections into the zone of cell columns; and consequently the spongy bone does not consist of long narrow tracts of bone, but rounded holes like a gutter formation. These tracts of bone are narrower than normal, and contain no cartilage remains, but also no osteoid tissue, which is usually found in rickets, but contain well calcified concentric lamellae. Another very striking anomaly consists in a too early development of the fatty marrow in the upper marrow spaces adjoining the cartilage, which is markedly deficient from the too long persistence of the red marrow in rachitic bones.'

*The condition of the remaining organs.*

In an account of a post-mortem examination on a Kalmuc idiot, quoted by Sutherland, aged 6 months, the right ventricle was hypertrophied, and there was non-closure of the interventricular septum. In another case, aged 13 months, there was a patent ductus arteriosus and an hypertrophied left auricle. John Thomson reports that he found in one case tricuspid incompetence, due to intra-uterine endocarditis.

With regard to the remaining organs, very little appears to have been found. At an autopsy performed at Paddington Green Hospital on an infant who died with an imperforate anus, the left kidney was cystic, the left ureter dilated, and the bladder hypertrophied; in addition there was also stricture of the second part of the duodenum. Heinman reports a case in which the liver was much enlarged, but he expresses no opinion as to what this increase in size was due to.

The following is a list of the chief congenital abnormalities which have been seen in cases of Mongolism, which I have collected from the literature on the subject:—

Nystagmus and strabismus.

Smallness of the naso-pharynx (Sutherland).

Umbilical hernia (Sutherland, Muir, and others).

Shortness of thumb and little finger, with anatomical anomalies of the bones (West and others).

Club-foot (McJackson).

Imperforate anus (Paddington Green Hospital).

Talipes valgus (Fennel).

Degenerate ears (Bourneville and Weygandt).

Testicles—(*a*) Small (Bourneville);
(*b*) Undescended (Author's Case 8);
(*c*) Cryptorchidism (Muir).

Absence of the nasal bones (Fraser).

Displacement of the nasal septum.

Undue backward displacement of the vomer (Still).

Extra lobes in the lungs (Bourneville, and see Case 6).

Hare-lip (Muir).

Contraction of the palmar fascia (Muir).
Webbing of the toes (Muir).
Supernumerary toes (Muir).
Polydactylism (Muir).
Naevi (Muir).
Phimosis (Muir).
Spina bifida occulta (quoted by Muir).
Congenital divarication of the recti abdominis (Author's Case 2).
Congenital dilatation of the colon (reported to me by a practitioner).
High vaulted palate (most observers).
Persistence of the metopic suture (Fraser and Bourneville).
Bilateral exophthalmos (Paul Lang).
Irregularity in the length of the toes (Fraser).
Congenital cataract (Author's Case 5).

*An account of two cases with Autopsies.*

*Case V. Family History.* The mother, aged 24 years, was married at 19; a thin, delicate, worn-looking woman; no evidence of alcohol, tubercle, or syphilis was obtained. Her parents were alive and healthy; an only brother died three months previously of consumption; she had one sister who was in good health. Owing to her husband's illness she had had to support the family, and during the period of her last pregnancy she was very often able to procure only one meal a day.

She stated that at the time of the conception of the idiot her husband was in very bad health. She had been pregnant twice, and there had been no miscarriages; the labours had been normal. The first child was a boy aged three, healthy but thin; the second, a girl, the patient.

The father, aged 27, married at 22; had been out of work for the last four years; his doctor stated that he had a 'fatty heart'. His father died of bronchitis, and his mother was alive and healthy; he had two brothers and two sisters, all in good health.

*Physical Examination.* The patient had all the typical characteristics of a 'Mongolian' idiot. Brachycephaly with sloping occiput; oblique palpebral fissures, marked epicanthus; short nose with a broad depressed bridge; protruding tongue, no enlarged papillae or fissuring; ruddy cheeks; no nystagmus or strabismus, but there was congenital cataract; the hands and feet were 'stubby'; the abdomen markedly protuberant, with a small umbilical hernia; no evidence of congenital heart disease was found. The child was admitted into hospital for an operation for the cataract.

Twenty-two hours after the operation of needling the respirations became much increased, and though examination of the chest was negative, it was thought that there might be broncho-pneumonia present: without, however, any further signs or symptoms developing the child died very suddenly, thirty-six hours after the operation.

The *Autopsy* was performed sixteen hours after death. Rigor mortis was present. The body measured 28 in. in length. The head measurements were:—

| | |
|---|---|
| Fronto-occipital circumference . . . | 16 in. |
| Transverse diameter . . . . . | 9·5 in. |
| Antero-posterior diameter . . . . | 10 in. |

The anterior fontanelle was wide open; the posterior closed; the sagittal

suture was open. The hard palate was markedly arched, the sides sloping very steeply anteriorly.

The calvarium was next removed. The dura mater appeared normal; there was no excess of cerebral fluid; the brain was removed and placed in a 10 % solution of formalin in normal saline. The base of the skull showed nothing abnormal.

The lungs and heart were normal.

The thymus and thyroid gland, both of which were of good size, showed nothing abnormal in consistency or on section, and were preserved for histological examination.

The liver and spleen were normal: the kidneys showed lobulation and were normal. The supra-renal bodies were preserved for examination. A portion of a costo-sternal junction was excised and preserved for histological examination. The upper dorsal region of the spinal cord was also removed.

The brain weighed 730 gms. (normal weight for this age being 727 gms., R. Boyd). The pia arachnoid appeared normal and was nowhere thickened or oedematous or unduly vascular, and stripped easily from the convolutions, except on the upper part of the Rolandic fissure and ascending parietal convolution on the left hemisphere, where there were a few points of adhesion. The vessels, nerves, and mammillary tubercles were symmetrical. The bulb, pons, crura, and cerebellum appeared normal.

The right hemisphere as a whole was slightly shorter in the antero-posterior diameter than the left. The frontal lobes were well formed; the left temporal lobe was somewhat smaller than the right. The Rolandic and Sylvian fissures on both sides were well marked. The ascending frontal gyrus on both sides was sufficiently developed, as was also the superior frontal convolution. The inferior and middle frontal gyri were better developed on the right side than on the left. The sulcus paramedialis was absent from both hemispheres.

The gyri of the orbital surfaces on both sides were exceedingly simple in character, and this simplicity of development was more marked on the left side. The rectal gyrus on both sides was ill developed. The convolutions of the mesial surfaces were exceedingly simple in character. The ascending parietal convolution was well formed on the left hemisphere, that on the right was much less bulky in its upper two-thirds. The supra-marginal, the angular, and the posterior parietal gyri were sufficiently developed. The superior parietal lobule was much smaller on the left than on the right side. The convolutions on both the external and mesial surfaces of the occipital lobes were abnormally flat; the principal fissures were well marked. The convolutions of the temporal lobes were much flattened. The island of Reil was well formed and the opercula developed. The corpus callosum and ventricles were normal. Sections of the hemispheres showed that the cortex was everywhere thinner than normal, this thinning being most marked in the frontal region. The major sulci appeared to be of normal depth, but the secondary fissures were very shallow.

Sections were prepared from the second frontal convolution and stained with iron alum haematoxylin and eosin.

There was no alteration in the pia arachnoid. No evidence was found of any inflammatory process, such as round-celled infiltration of either the perivascular or pericellular strata, nor was there any increase in the neuroglia tissues. There was no thickening of the vessel walls. The most striking feature was the manner in which the nerve cells had contracted away from the surrounding walls. This might have been due to post-mortem changes or to methods of fixation, but not altogether, for cells were seen which were not so contracted. There was relatively a smaller number of large pyramidal cells than normal. The remaining cells showed nothing abnormal.

Portions of the cortex were also prepared by the Weigert-Pal method and the fibres examined. On removing the sections from the haematoxylin solution,

there was no evidence of the white matter having been mordanted. The process was repeated, but with a similar result.

*Sections of the spinal cord* were stained with Pappenheim's stain and with polychrome methylene blue, to show the cells, and others treated with the Weigert-Pal method. Beyond the fact that there appeared to be fewer motor cells in the anterior horns than normal, nothing else was discovered. Nissl's granules stained well, and there was no disintegration. The nucleus and nucleolus showed nothing pathological. There was no evidence of any inflammatory process in either the cord or its membranes. The various fibre tracts (direct and indirect pyramidal) were differentiated and appeared to be of normal bulk. The only point to be noticed was that the nerve sheaths appeared to be thinner than normal.

Sections of the supra-renal capsules were stained with eosin and haematoxylin. After careful examination nothing abnormal could be detected.

Sections of the thymus gland were stained with Pappenheim's stain and with polychrome methylene blue. Both the cortical and medullary portions of the gland appeared quite normal, and there were no pathological changes to be found.

The thyroid gland was stained with Pappenheim's stain and polychrome methylene blue. The capsule was a little thickened. There was a diminution in the size and number of the vesicles, though they were lined with regular cubical epithelium, and filled with colloid material which took the stain well. The interstitial tissue was much increased, and there was much round-celled infiltration. The vesicles in parts were seen to be invaded by these round cells. There was sclerosis of the gland.

Sections of bone and cartilage were examined. The layer of proliferating cartilage cells and the layer of parallel cell columns showed nothing abnormal. There was no irregularity of calcification, and no excess of red marrow.

### *Case VI.—M. G., female, aged 8 months.*

*Family History.* The mother, aged 41 years, was a bright, intelligent, healthy woman; she had no signs of tuberculosis, syphilis, or alcohol; she was not related to her husband before marriage, had always had good health, and had had nine children. The first, second and fourth children were boys, alive and healthy; the third child, a girl, died of diarrhoea; the fifth, sixth, seventh and eighth children were healthy girls; the ninth was the patient, a female aged 8 months. She had had no miscarriages. The mother's health during the last pregnancy was good. All the labours were normal. The father, aged 42 years, strong and healthy, showed no sign of tuberculosis, syphilis, or alcohol; the remainder of his family were, he said, healthy.

The patient was brachycephalic, with steep occiput. Measurements:—

| | |
|---|---|
| Fronto-occipital circumference . . | 14·5 in. |
| Transverse diameter . . . . | 8·75 in. |
| Antero-posterior diameter . . . | 9·5 in. |
| Tragus—glabella . . . . . | 4 in. |
| Tragus—mid-occipital point . . . | 4·5 in. |

The ears were normal; there was a moderate quantity of fine bright hair; the anterior fontanelle wide open, posterior slightly.

The face was characteristic; 4 in. broad, 4½ in. long. The nose was short with depressed bridge, and the anterior nares rather wide. The cheeks were fat, the complexion pale, the palpebral fissures oblique; there was no nystagmus or strabismus, but a slight epicanthus was found; the fundi were normal. The lips were rather pouting, and the lower one was marked by transverse furrows.

The tongue was constantly somewhat protruded, and tongue-sucking was observed frequently; there was no enlargement of the papillae or fissuring. There were no teeth, and the palate was moderately arched.

The chest was normal; there were no signs of rickets; the heart was normal. Examination of the lungs showed that there was bronchitis. The abdomen was rather prominent and presented a small umbilical hernia; the external genitalia were normal. The spine showed none of the normal curves. The extremities were of normal proportions; the hands and feet were normal; no curving of the little fingers was present, and no abnormal mobility of the joints.

The patient measured 21 in., weighed 21 lb. and was poorly nourished; she was breast fed. The temperature varied between 97·8° and 98° F.; the skin was smooth and white; obstinate constipation was present.

The patient could not hold up the head, and had shown no sign of intelligence; she never smiled or cried, and took no notice of the mother.

The plantar reflex was extensor; the knee-jerks were absent; the pupils reacted to light.

The child was admitted into hospital a few days later, suffering from acute broncho-pneumonia, and died in eight days.

The *Autopsy* was performed fourteen hours after death. Rigor mortis was present.

The anterior and posterior fontanelles were open, and the metopic suture persistent. The lambdoidal, squamous, and sagittal sutures were open.

The dura mater was normal, and there was no excess of cerebral fluid. The brain was placed in a 10% solution of formalin in normal saline. A thorough examination of the base of the skull failed to reveal anything abnormal.

There were about 3 drachms of pus in the left pleural cavity; both lungs were the seat of broncho-pneumonia, and there was a patch of lobar consolidation at the left apex. The right lung consisted of four lobes—the fourth lobe being brought about by the division of the middle lobe, the extra lobe having its own bronchus. The bronchial glands were slightly enlarged. The heart was normal; the foramen ovale was still patent; the thymus and thyroid glands, which were of normal size for the child's age, were kept for histological examination.

The liver, kidneys, and spleen were normal. The supra-renal capsules were removed for examination.

The brain weighed 622·8 gms. (Average weight for this age = 727 gms.) The pia and arachnoid stripped easily, and nowhere were there any points of adhesion; the cranial nerves, vessels, and mammillary tubercles were symmetrical; the pons medulla, crura, and cerebellum were of normal size. The right hemisphere was slightly broader in the transverse diameter than the left, and the occipital poles were wider apart than normal, so that upon looking vertically down upon the convexity of the brain it was possible to see the lobes of the cerebellum. Upon a general view of the hemispheres it was at once seen that the gyri posterior to the Rolandic fissure were much flatter than those anteriorly.

The principal fissures, the Rolandic, Sylvian, posterior occipital, calcarine, calloso-marginal and collateral, were well marked on both sides, but the minor sulci were with difficulty made out and in many cases could not be traced. On the left hemisphere the Rolandic fissure was divided into two by an annectant gyrus. In a normal brain this annectant gyrus is seen by separating the lips of the fissure, lying at the bottom of the sulcus connecting the two walls. Cunningham states that the presence of this gyrus upon the surface of the hemisphere is an indication of the persistence of the foetal state. On the right side the ascending frontal convolution was fairly well marked, and was cut into at its upper extremity by the superior precentral furrow. On the left side it was not so well marked in its upper half. The three frontal convolutions on the left side were more prominent than those on the right. The sulcus

paramedialis was absent from both hemispheres. The temporal lobes were well formed, the sulci well marked, but the convolution simple and much less bulky than normal. The orbital sulcus on the right side was Y-shaped, and that on the left H-shaped. On the left side the rectal gyrus was absent.

The gyri of the parietal and occipital lobes were extremely simple in character and much flattened; and the mesial surfaces presented the same appearances.

The basal ganglia, ventricles and corpus callosum showed nothing abnormal. Sections through the hemispheres showed that the cortex was thinner than normal, and this appeared to be most marked over the parietal and occipital lobes. The sulci were distinctly shallower than normal.

Sections of the brain stained with Pappenheim's stain and with polychrome methylene blue were examined from the three areas of the left hemisphere. There was no evidence of any inflammatory process, such as round-celled infiltration or increase in the neuroglia tissues, nor were there any changes observed in the pia arachnoid. No thickening of the coats of the blood-vessels was seen, as described by Bourneville. Meynert's layers were quite distinct. All the nerve cells were somewhat shrunken in their spaces, but this was not so marked a feature as in Case V. The cell nuclei were quite definite, and Nissl's granules well stained and showed no evidence of disintegration; there was no brown pigment in the cells. The large pyramidal cells were certainly less numerous than normal in all three areas, and this diminution was most marked in the frontal region.

Portions of the formalin-fixed material were transferred to Weigert's chrome alum copper acetate mordant and the fibres examined. The mordant was frequently changed and the duration of mordanting was about a fortnight at a temperature of about 30° C. The brain sections when removed from the haematoxylin showed no evidence of the white matter having been mordanted. All the sections were therefore remordanted at 30° C. in Weigert's chrome alum potassium bichromate mordant. Nevertheless the white matter still remained unmordanted in the brain sections, although the cord sections (of Case V) were quite satisfactory.

No conclusions, therefore, could be drawn about the state of the fibres from the examination of the portions of the brain, or that of Case V, for it was hardly possible that there was no myelination of the fibres in either case.

I regret that further examination, in order to clear this point up, was not possible, as both brains had inadvertently been allowed to become dry.

## CONCLUSIONS.

In the majority of instances Mongols are born towards the end of a large family, and both parents are generally over the age of 40 at the time of the birth; in an appreciable number of cases there is a history of bad health in the mother during her pregnancy. In no way has syphilis, parental alcoholism, or tuberculosis been proved to have any share whatever in the causation of the condition. As all cases of Mongolism have precisely the same physical characteristics, it is reasonable to assume that it is due to a special and specific factor—in the same manner that cretinism is in every case due to a defective function and pathological change in the thyroid gland.

Mongolian idiots form about 3–5 % of all classes of idiots. That Mongolism appears to be less common on the Continent is probably due to the fact that Continental observers have been much behind the English in recognizing this form of idiocy.

No further reference need be made to the characteristics of this variety of idiocy. One point, however, I should like to emphasize, with regard to the condition of the various nerve reflexes as exemplified by my own cases. The plantar reflex was extensor in every case, and the knee-jerk was absent in six and diminished in one. The cutaneous reflexes were sluggish in all, and the eye reflexes were normal.

They are to be diagnosed solely by their physical characteristics—in the early years by their features alone, and in addition in the later years by the characteristic appearance of the tongue. The condition is easily recognized at birth. The other conditions with which Mongolism is most likely to be confused are achondroplasia, cretinism and rickets. (See Figs. 5 and 6.)

In the literature I have met with the accounts of twenty post-mortem examinations. The chief lesion is situated in the brain, and there is no evidence that premature ossification of the basal bones of the skull is responsible for the cerebral changes. Macroscopically the brain is characterized by simplicity and aplasia of the convolutions. In some cases observers have reported gross anatomical deformities. In the majority of cases there are pathological changes in the cortex. These consist of thinning of the cortex; scarcity of myelin fibres, with great variation in their direction, this being most marked in the tangential and radial fibres; and rarefaction of the nerve cells, especially of the large pyramidal cells. In addition to the above changes, some observers have also described fibrous meningitis. One observer only, after making a microscopical examination of the brain in several cases, has described it as being normal. All observers are agreed that there is no evidence of acute inflammation.

There are no reports upon the spinal cord in Mongolism in the literature. In my own case there appeared to be fewer cells than normally in the anterior horns, and the nerve sheaths to be somewhat thin. The various tracts appeared to be of normal bulk. The membranes were normal.

With regard to the ductless glands, the thymus has always been found to be normal. In one case only has anything pathological been found in the suprarenals, and these changes were of a necrotic nature. In several instances morbid changes have been discovered in the thyroid gland—degeneration of the colloid matter and sclerosis of the gland. I found evidences of sclerosis in this gland in my first autopsy; but as yet there is no evidence that any alteration in either the structure or function of the thyroid gland can be held to be responsible for this form of idiocy.

There is delayed ossification of the bones, but on histological examination no other changes are discovered.

Evidence of congenital morbus cordis is present, as far as can be ascertained, in about 10% to 20% of the cases.

Various other congenital abnormalities are often present, but they are to be looked upon as accidental and of no direct relation to the condition. They occur much more frequently in the Mongolian than in any other variety of idiocy. Probably they indicate some influence acting very early in intra-

uterine life, about the second month, and may be synchronous with the cerebral changes.

The prognosis is in all cases very bad, mentally as well as physically. It would probably not be an exaggeration to say that fully 70 % die before the onset of puberty. The cause of death is usually bronchitis, broncho-pneumonia, or tuberculosis. A few, however, appear to die from pure inanition.

There is no drug treatment. Extract of the thyroid and thymus glands is of no avail; and pedagogic treatment is of avail up to a certain point only.

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## DESCRIPTION OF FIGURES.

PLATE 7, FIG. 1. Mongol, aged 18 months. Showing protrusion of tongue and everted lower lip and oblique palpebral fissures.

FIG. 2. Mongol, aged 3 years.

PLATE 8, FIG. 3. Mongol, aged 5 years. Characteristic profile and prominent abdomen.

FIG. 4. Mongol, aged 3 years. Characteristic head.

FIGS. 5, 6. Achondroplasia.

FIG. 7. Hand of Mongol, aged 8 years. Ossification advanced to fifth year only.

FIG. 1

FIG. 2

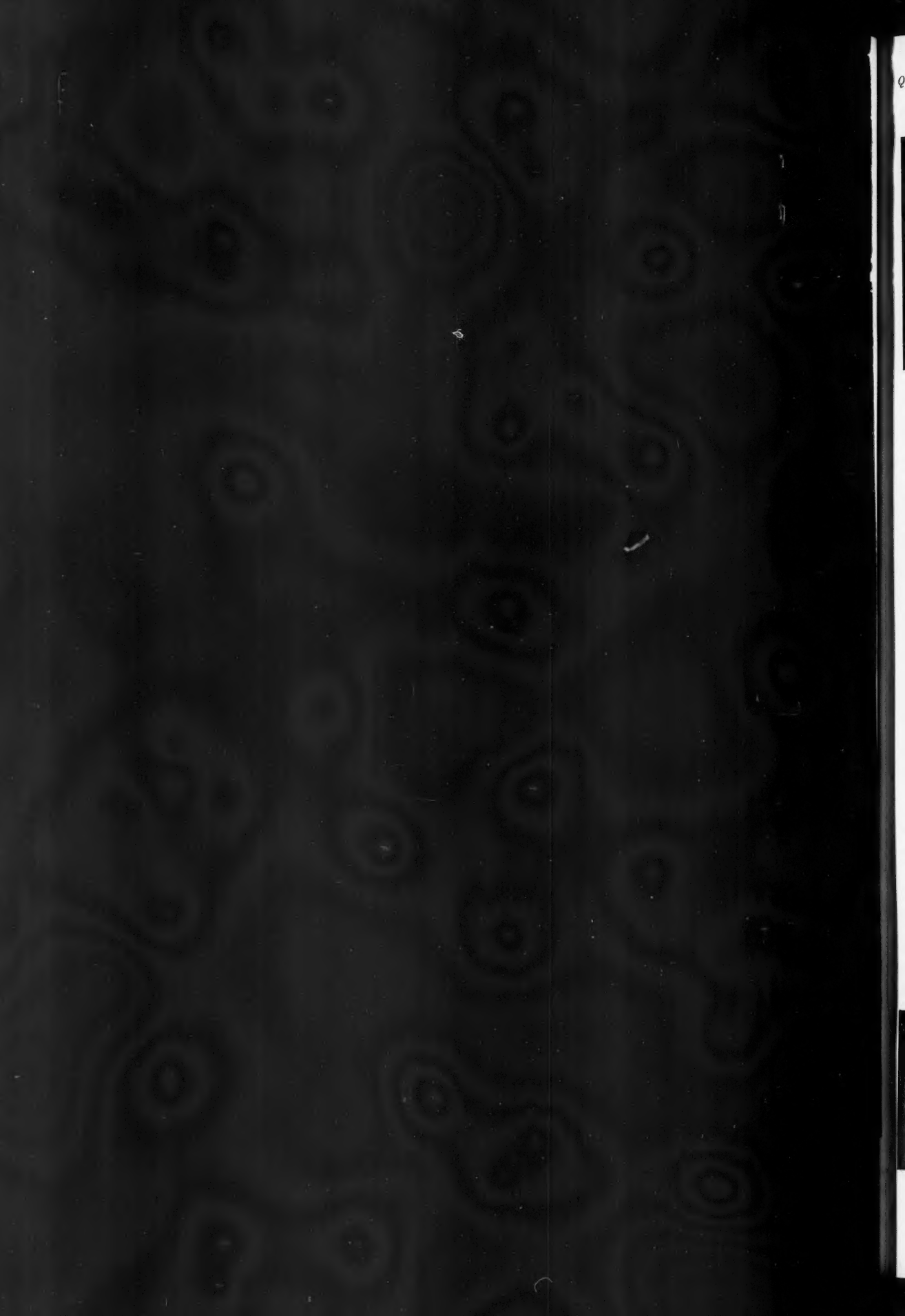

FIG. 3

FIG. 5

FIG. 7

FIG. 4

FIG. 6

# THE MEDICAL ASPECTS OF PYELITIS IN PREGNANCY[1]

By E. WARD

Since Rebland's lecture on 'Pyelitis in Pregnancy' in 1892, this subject has attracted considerable attention in France, and many papers have appeared in the French medical journals. It is only lately that interest in the subject has arisen, chiefly among obstetricians and surgeons, in this country and in Germany. The malady is, however, of considerable importance to physicians also, for medical treatment is usually sufficient to cure the disease; obstetrical treatment is only occasionally necessary, and surgical treatment is called for more rarely still. Furthermore, to avoid errors in diagnosis a knowledge of pyelitis is essential to the physician; and the relations of the disease to other forms of pyelitis are of considerable interest,—to that pyelitis, for instance, which is met with in children, and to the acute coli pyelitis which sometimes occurs in men.

The name used for the disease by most authors is pyelonephritis of pregnancy, for, as they point out, the kidney substance is usually infected sooner or later, and it is impossible to say when this takes place. But it is also true that the bladder and the ureters are affected, and often also the urethra; so that the correct name for the disease becomes cysto-uretero-pyelonephritis, as suggested, indeed, by a German writer. If this name, although correct, is too unwieldy and ugly for use, why should we not speak simply of pyelitis? To simplify the terminology further it would perhaps be allowable to speak of the disease, the pyelitis of pregnancy which has come to be so well recognized, as *Encyopyelitis*; and to reserve the name *pyelitis in pregnancy* for those cases in which pyelitis occurs in pregnancy owing to some previous disease which might well have caused it at some other time. For there are many conditions, such as a hydronephrosis, renal calculi, or a congenital kink in the ureter, which may easily cause pyelitis at any time; and in pregnancy the diseased kidney, far from being immune, is more liable to be attacked. It must be admitted, however, that in an individual case it is often difficult to distinguish between pyelitis in pregnancy and Encyopyelitis, if we are thus to name the pyelitis of pregnancy.

### *Aetiology of the disease.*

There are—(1) a predisposing cause; (2) a cause which actually excites the disease.

(1) Pregnancy is the chief predisposing cause, and we have to consider briefly why pregnancy disposes to this disease. There is a partial blockage of one or both ureters, usually at the pelvic brim, and probably because at the fifth or sixth month of pregnancy, when the disease generally occurs, the greatest circumference of the uterus is then opposite the point where the ureter

[1] Founded on a thesis presented for the degree of M.D. in the University of Cambridge.

[O. J. M., Oct., 1908.]

crosses the pelvic brim. There are other important predisposing causes besides pressure. The condition of the kidney may be altered. Apart from a previous attack of scarlatina or other specific fever; of nephritis or haematuria due to whatever cause; the effect of the toxaemia of pregnancy must be considered. If the view is correct that eclampsia and acute yellow atrophy of the liver are both due to the same cause, and that cause is the absorption of some toxic product from the uterus, it follows that, short of such a severe condition, minor degrees of toxaemia may occur. In these cases the kidney is injured by the excretion of the toxins and pyelitis is rendered more possible. It is interesting to note in this connexion the confusion that exists in the differential diagnosis between Encyopyelitis and the albuminuria of pregnancy. There seem also to be a number of cases of albuminuria, some even of eclampsia, which develop in addition an Encyopyelitis.

There is probably also some alteration in the urine in pregnancy which allows the growth of organisms to take place in it more readily than at other times. Barnard gives some information he obtained from Wright. 'The bacillus coli communis,' he says, 'grows in an alkaline or neutral medium by preference, but can grow in an acid medium. There is in urine a factor inimical to the growth of organisms, and this factor belongs, perhaps, to the class of opsonins found in serum and the other fluids of the body. Bacteria grow infinitely more readily in the urine of a case of coli cystitis than in a normal urine. In the one case the urine incubated for twenty-four hours will contain 300-400 millions per c.cm., while normal urine incubated for the same time will contain the same number of thousands.' This was not written with special reference to Encyopyelitis, but only to cases of coli pyelitis, and it may be that the organism alters in some way the condition of the urine in which it lives. The facts are of interest here, for nearly all Encyopyelitis is due to the bacillus coli. The cases of Encyopyelitis occurring early in pregnancy, during the first or second month, either with or without a previous attack, must be explained as dependent on an alteration in the urine, or by an increased vascularity; for at this time the uterus is not large enough to exert pressure.

Lastly, among the remoter causes should be mentioned any incident which lowers the general or local resisting powers of the patient; such, for instance, as hard work, cold, influenza, gastro-enteritis, or injury. It may here be stated that in some cases the resistance of the patient does not seem lowered sufficiently during pregnancy to allow the outbreak, and the illness begins in the puerperium.

(2) To consider next the exciting cause of the disease, the micro-organism. First of all we must decide what organism is present. Four are in the accounts of cases here considered: bacillus coli communis, staphylococcus pyogenes aureus, streptococcus and gonococcus. Of 56 cases in which definite mention is made of the organism found, in 44 this is bacillus coli communis, in 9 a streptococcus, in 2 staphylococcus, and in one only is the gonococcus definitely mentioned.

Mirabeau in a recent paper mentions all the above organisms and adds bacillus tuberculosis to the list. I have not been able to find any mention of bacillus tuberculosis in the literature as a cause of Encyopyelitis, though there are cases recorded, not unnaturally, in which a tuberculous kidney has become infected with bacillus coli during pregnancy. Acute renal tuberculosis would be no less likely to occur in pregnancy than at other times, and I have seen recorded a case in which this happened in the puerperium. It is mentioned not infrequently that 'many bacteria were found in the urine', without more definite specification; or the names of several organisms are mentioned. It is certainly probable that the infection may be a mixed one in many cases, but it was hard to find in the records sufficient definite evidence of this from which to compile statistics.

With reference to the gonococcus as a causative agent, there are undoubtedly many patients, especially in the list given by Marteville, who have had gonorrhoea and who develop an Encyopyelitis; so that one in fifty-six may not represent accurately the frequency of its occurrence. Baisch, in speaking of bacillus coli, says that it passes up the urinary tract as a parasite after staphylococci or other pyogenic organisms have led the way. In the case of the other pyogenic organisms the event does not seem to be proven, but it certainly seems as if the gonococcus could precede bacillus coli and produce a cystitis, and then afterwards the second species may pass on to the ureters, and ultimately cause a coli pyelitis.

It should be noted that mistakes may arise here, as in other cases, because it is not remembered that other organisms besides gonococcus may cause urethritis. In one of the French cases it is remarked that the case was probably gonorrhoeal because the husband of the patient had suffered from a slight 'échauffement'. Now this term seems to be generally used for a slight subacute urethritis different from the acute affair which follows a gonococcal infection. So that the evidence in this case is insufficient.

Next to consider how the organisms reach the pelvis of the kidney. They may get there from the blood stream, and thence descend to the bladder; they may reach the bladder first and then ascend; or they may get to the kidney by the lymph stream. The majority of French writers have supposed that the infection usually follows a descending course. Opitz and other German writers believe that the ascending course is commoner, though they do not deny that a descending infection may occur. The weight of the evidence seems to be with the German writers, for the following reasons:—First, the onset of the symptoms of pyelitis is generally preceded, or accompanied, by those of cystitis: the number of cases presenting bladder symptoms may be estimated at 65%. Secondly, only one kidney is affected as a rule; should two be affected the one precedes the other. No other organ in the body, moreover, shows signs of infection, except in rare cases. Furthermore, nephrectomy procures immediate recovery; this we should not expect if the kidney disease was only part of a general infection. It is important to note that Opitz failed to obtain the infecting organism from the blood in cases of Encyopyelitis. The belief of the

French authors is founded mainly on two series of experiments, on some experiments by Rebland and Bonneau and on some by Posner and Lewin. In the experiments of Rebland and Bonneau the ureters of four rabbits were tied, and into the ear veins of two of them bacillus coli was injected, into the veins of the others streptococci. In each case the rabbits developed pyelonephritis, due in the first pair to bacillus coli, and in the second pair to streptococci. In the other experiments, those of Posner and Lewin, a pyelonephritis due to bacillus coli was obtained after ligature of the rectum and urethra. It is also pointed out by the upholders of a descending infection that bladder symptoms are not always present, and that diarrhoea or constipation commonly precedes the attack. But, on the other hand, the experiments of Rebland merely prove it is possible for a blood infection to give rise to a pyelonephritis, a theory that is not denied by those who say the ascending route is usual in Encyopyelitis. Opitz considers that too much importance has been attached to the experiments of Posner and Lewin. He says that no micro-organisms are to be found in the blood after ligature of the bowel; nor are micro-organisms present in the fluid obtained from the sacs of strangulated hernias. Faltine also failed to confirm the experiments of Posner and Lewin: with ligature of rectum and urethra he obtained a cystitis only; and this effect was produced by ligature of the urethra alone.

The absence of any record of cystitis before the pyelitis does not disprove that the pyelitis is due to an ascending infection, for cystitis and urethritis are very common in women, especially during pregnancy. They may have been present and passed off, and have been forgotten; or the organism may be present in the bladder and cause no symptoms owing to a local immunity; although it gives rise to a severe ureteritis on reaching the ureteral mucous membrane. That organisms are frequently present in the bladders of women without causing symptoms is shown by the attacks of cystitis which the practitioner is not infrequently called upon to treat when a cold wind is prevalent. Constipation or an attack of diarrhoea may enhance the virulence of the organisms in the secretion of the vulva, where the bacillus coli is usually to be found. Attacks of diarrhoea, too, may well lead to direct contamination of the vulva with a micro-organism coming from the rectum.

If it be granted that the bacillus coli, which usually causes Encyopyelitis, follows an ascending path, we have next to decide how the organism finds its way upwards. The short urethra of women is a less efficient guard for the bladder than the long urethra of men; but when the organism is in the bladder there is still the valvular action of the ureteral orifice to be overcome, an action which is said to be increased in cystitis by muscular spasm at this orifice. To find a probable explanation of the manner in which the organism surmounts this difficulty we must turn to the experiments made by Bond of Leicester, detailed in his address to the British Medical Association in 1905. Bacillus coli does not ascend in the stream of urine, but passes upwards in the mucous membrane itself to the stagnant pool of urine above the obstruction. If sterilized indigo granules are applied to the orifice of various mucous passages, they are

found to ascend in the face of the stream of contents. For instance, indigo was applied to the lips of the uterus and in a day or two granules were found in a pyosalpinx; in other cases they were found in the peritoneal cavity near the ostium abdominale. Indigo was placed in the rectum, and three days later it appeared in a caecotomy wound; while indigo placed in the bladder was recovered from a fistulous ureter in the loin. The motility of the organism may be another factor which helps it to ascend; bacillus coli is certainly the commonest infective agent in kidney diseases apart from pregnancy.

It should be emphasized here that for an acute ascending pyelitis an obstruction to the flow of urine is not essential. In the first case mentioned by Barnard, a young man, without previous symptoms, was suddenly attacked with scalding micturition and severe hypogastric pain, followed by pyrexia and severe pain in the right loin, for which nephrectomy was performed. The history is very similar to that of an Encyopyelitis of an acute type; but there was nothing to show that any stagnation of urine had occurred. If this is possible in a man because of some increased virulence of the infecting organism, how much more is it likely to occur in a pregnant woman.

A dirty catheter is sometimes blamed for the disease, and such an instrument might easily cause a cystitis; but its importance is probably overestimated.

That descending infections do occasionally occur in pregnancy it would be idle to deny. Gosset records a case where the disease followed a mammary abscess. There are also cases occurring in the puerperium, two of which are included in my list, where the infection takes place by the lymphatic route from a parametritis.

*The age of the patient and the period of onset in pregnancy.*

A graphic representation of the age of onset in 184 cases in which this was mentioned is seen in Fig. 1.

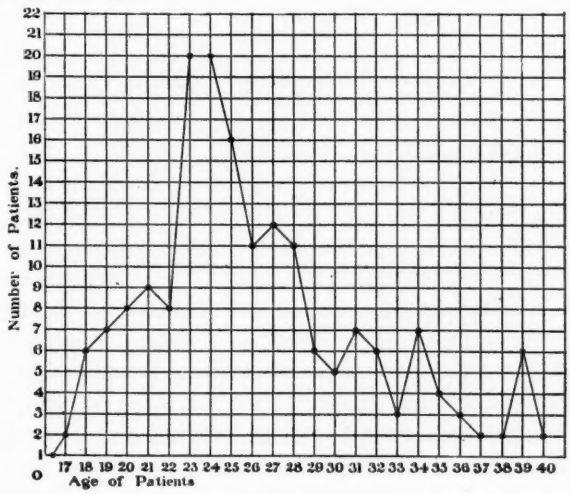


FIG. 1.

A graphic representation of the period in pregnancy at which the onset occurred in 187 cases is seen in Fig. 2.

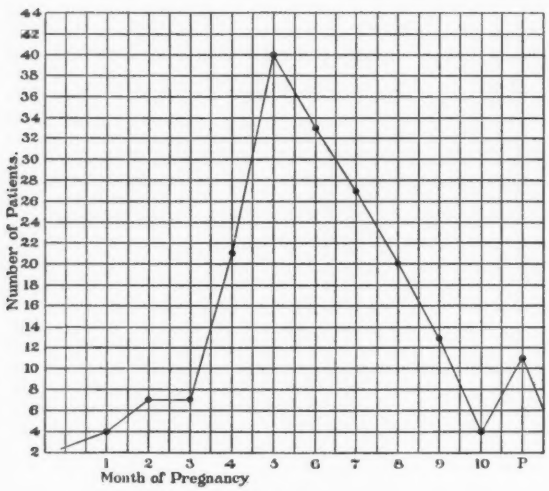


FIG. 2.

An error that creeps into this list is the relapse in the later months of cases which occurred early. I have eliminated this as far as possible by considering any case in which there was mention of earlier symptoms as beginning at the earlier date.

The frequency of second attacks of the disease may be considered here. From the cases collected it would appear a moderate estimate to say that 15 % to 20 % of the patients have a relapse at a later stage of the same pregnancy, and 8 % have an attack in a succeeding pregnancy.

### *Symptoms and course.*

Clinically the disease presents an extremely variable picture. It would be well to describe first a typical case of the acute form, of the chronic, and of the subacute form; then to deal with such variations as may occur.

In an *acute case* after exposure to cold, after an attack of gastro-enteritis, or other incident, but often with no such intercurrent cause, the patient is suddenly seized with a severe burning pain on micturition, with strangury and with general malaise. Vomiting follows, and there are rigors, which may be repeated. Severe pain rapidly comes on in the right lumbar region and in the hypogastrium; there may also be anterior renal pain which may shoot down into the groin and along the inner side of the right thigh. Exacerbations of the renal pain occur, and possibly renal colic. There is loss of appetite and great thirst; the bowels are confined, or more frequently there is diarrhoea. The temperature is high and oscillating. On examination of the patient the tongue is found to be thickly

furred and the pulse moderately rapid. The abdomen is markedly tender in the hypogastrium and in the right posterior renal position; there is also muscular resistance in the right loin, and possibly some puffiness. The kidney, if felt, may be enlarged. The quantity of urine passed is variable; at first there is usually a small amount of dark coloured urine, later a large quantity is passed; it is then pale yellow and slightly cloudy. The microscope shows pus cells, epithelial cells, and many motile bacilli. In a few days severe pain may occur in the left-kidney region. At the end of a fortnight the temperature falls and the general condition improves. Or deterioration may continue rapidly, with wasting, a cough, and a hectic temperature. In any case the urine will still contain pus after the general condition has improved.

A word further about the abdominal and pelvic examination will not be out of place. If pregnancy has far advanced it is difficult to palpate the kidney. This is best attempted with one hand, the thumb anteriorly, the fingers posteriorly in the angle between the last rib and the erector spinae. The hand used would be the left for the right kidney, while the right hand pushes the uterus on one side to ensure the left thumb getting round the outer side of the uterus, and so prevent the inclusion of some of the uterine wall in the grip of the left hand. The kidney, as has been said, if felt, may be enlarged. This enlargement is rather difficult to estimate, and it is common to report that a kidney is enlarged if it is palpable, especially when two hands are used for the purpose: the thick abdominal wall gives to the examining hands a false impression. The kidney very commonly is noticed to be more movable than is normal.

There may be also a tenderness in the right iliac fossa, and often this is most marked over McBurney's point, the point where the ureter crosses the brim of the pelvis. *Per vaginam* in an acute case, there will be probably nothing noted beyond, perhaps, tenderness at the point where the ureter enters the bladder, and of the base of the bladder itself. There is no typical temperature chart in these cases. Certain authors have published, it is true, a small series of cases with charts so similar that they declared them to be typical of the disease. But in considering a large number of cases, the recurrence of a certain form of chart in a few instances may give the impression of a type, and yet, on continuing the investigation, the recurrence is seen to be only a coincidence. The temperature may fall by lysis or by crisis.

In a *chronic case* the onset is so insidious that the patient cannot say exactly when she began to be ill. The disease is frequently preceded by a slight albuminuria, but this will probably have escaped notice. There are languor, pallor, anorexia, and constipation. Frequently no pain is complained of in the kidneys, but there may be a sensation of heaviness in the loins and in the hypogastrium. There is occasional pyrexia, but there may be no rise in temperature at all during the patient's stay in hospital. There is wasting and there are night sweats. The kidney is slightly tender on palpation, but this may not be noticed till the second or third examination, or until after special attention is drawn to

the kidney by the discovery of pyuria. The tenderness is most noticeable at the hilum, and if therefore pressure is made only to the outer side of the body of the kidney, this tenderness may be missed. Leucocytosis is usually present, and there is frequently a cough. The urine contains some pus and often granular casts. This form of the disease is usually mistaken for tuberculosis, and it is only when the patient is found to have become stout and well again some time after labour that any certainty about the diagnosis is attained.

The *subacute group* of cases is intermediate between those above described. The onset is gradual, as a rule, but there may be an occasional rigor. There is frequency of micturition with but little pain, and there is usually vague pain in the abdomen, chiefly in the epigastrium. There is continued fever, and tenderness in the region of one or both kidneys is present. This form of the disease is frequently mistaken for typhoid fever, as might be expected, perhaps, when it is remembered that the organism which causes it belongs to the same coli-typhoid group. The disease usually subsides on delivery, but may continue in one of the ways to be described later.

### *Variations of type.*

It is very common to get relapses. The patient seems quite well and treatment is stopped, or she is allowed to get up, and a relapse at once occurs; or the patient goes home, only to return as ill as ever in a week's time. The disease is again suitably treated, but again relapses, and the patient may only get well some time after delivery.

Another form of relapse is that which occurs in the ninth month of pregnancy when the disease was apparently cured in the fifth, and the patient has remained well since. Then we may get the relapse of an infection which had been considered cured, occurring in the puerperium; or, in the same period, we may get an acute exacerbation of a case which has hitherto been of the chronic type. A relapse at the next pregnancy is common enough: I have said elsewhere that it may be considered as occurring in about 8% of cases. The patient is especially vulnerable if the second pregnancy succeeds the first at rather a short interval; or if, as sometimes happens, there have been symptoms of urinary trouble from time to time between these two pregnancies. These relapses take place at an earlier date in the second pregnancy; at the second or third month, perhaps, or symptoms may even have been present since the date of the last menstruation. A previous kidney disease, not necessarily a pyelitis, occurring in a previous pregnancy, also causes an early onset of Encyopyelitis.

Vesical symptoms, as has been already noted, may be present or absent. If present, they may show very different degrees of severity; they may occur before or after the kidney symptoms, but more usually before. After myself seeing a comparatively small number of cases I was led to believe that the disease should not be diagnosed in the absence of early symptoms of cystitis. On the other hand, series of cases have been collected, by those who believe the

infection descends, in which the symptoms of cystitis were very slight or altogether absent.

As has been stated, the pain is usually right-sided and frequently remains only on the right side; it is, however, common for a right-kidney pain to be followed by pain in the left kidney after a time, or for a patient to come up again for treatment on account of a relapse in which the symptoms are now on the left side. Left-sided cases which remain so throughout the disease are exceptional. Of 187 cases where the side affected could be ascertained, in 107 the disease was confined to the right side; in 63 both kidneys were affected; and in 17 it was the left kidney alone. Translated into percentages this gives us roughly:—

55 % right kidney.
35 % both kidneys.
10 % left kidney.

These figures do not differ much from those obtained by Opitz from a series of 63 cases. Of these 42 were right-sided; in 12 both kidneys were affected; and in 9 the left alone suffered. When both kidneys are attacked the inflammation on one side nearly always precedes that on the other, but when first seen in hospital both may be already affected.

A variety of this malady met with from time to time, and not, perhaps, as uncommon as would appear from the published cases, is a chronic coli infection of the urinary tract, dating from some pregnancy, and lasting for years with occasional exacerbations, each of which subsides under appropriate treatment. These are generally considered to be cases of renal tuberculosis, and the clinical picture is certainly very similar. A good example of this may here be given.

A woman, aged 34, was seen after the birth of the third child. The patient was first taken ill while pregnant for the first time five years ago. There was frequency of micturition and pain in the abdomen and in the right lumbar region. She got better shortly after the birth of the child, but has never enjoyed quite good health since this time. The child lived only three days. There was a slight recurrence of the trouble towards the end of the second pregnancy, but a healthy child was born. In the third pregnancy there was another relapse; the patient appeared to recover after the child was born, but relapsed again one month after labour, when she began to get about again.

When the patient was seen a few months later, she complained of a frequency of micturition, every half-hour during the day and seven to eight times at night. The abdomen was tender in the right-kidney region and also in the hypogastrium; per vaginam the right ureter was felt as a thickened tender cord.

The urine was acid; specific gravity, 1,016; it contained pus, a little albumen and many motile bacilli. Much improvement followed treatment by rest in bed and the administration of urotropine. I diagnosed a coli infection of an old tuberculous kidney; but a urinologist who examined the patient with the cystoscope did not think the disease was tuberculous, though the right ureteral orifice was retracted.

I have since heard that the patient is now pregnant for the fourth time, and has had for five months severe pain in the left lumbar region. This appears to be one of the cases referred to where an Encyopyelitis passes on to a chronic inflammation of the kidney and ureter.

A French author, Bar, has written on the presuppurative stage of infection of the ureters in pregnant women. He says that suppurative pyelonephritis is only one manifestation of an infection of the urinary tract by the coli bacillus, and he suggests there may be a preceding stage beyond which many cases do not go, characterized by the presence of the coli bacillus in the urine and by clinical signs due to absorption of its toxines. The general symptoms are not so acute, he states, nor is the prognosis so grave as in the other forms. The variety of which he speaks I have intended to include under chronic Encyopyelitis. It is with pyelitis as with inflammation elsewhere; suppuration is not a necessary accompaniment. When pus appears it often means that the patient is developing a resistance to the infection: in the case of a severe infection of the finger, for example, as may take place in the post-mortem room, the general symptoms may be present, and enlarged axillary glands felt, before there is more than a superficial redness at the site of inoculation. With reference to Bar's remarks on the prognosis in this form of the disease, the cases considered here do not entirely support his views. The chronic cases frequently lead to a prolonged and severe illness; while in the acute cases, for the most part, the patients get rapidly better.

To consider for a moment whether the nature of the infecting organism alters the clinical type of the disease. On this point a conclusion would be premature, for as yet the bacteriology of the disease is too uncertain. At first, judging from a few cases only, there seemed to be a streptococcal type and a coli type, but a more extended experience has altered this impression. The clinical picture of a severe coli infection is much the same as that due to a streptococcus. In the case of staphylococcus, however, if it be allowable to judge from such very limited material, it may be said that these infections are usually severe, and are likely to call for operation later. Marteville states that cases due to gonococcus are slight and insidious and occur far more frequently on the left side than do the other infections. This may be so; it certainly seems to be that the preference for the right kidney found in a large number of cases is not borne out if the attention is confined to those not due to bacillus coli. But the matter is complicated because of the presence of a mixed infection.

### *Complications of Encyopyelitis.*

These may be most simply classed under two headings: those occurring in the urinary tract, and those occurring elsewhere.

A. *Complications in the Urinary Tract.* Cystitis, ureteritis, and urethritis occur too frequently to be considered complications: they are part of the disease; nephritis, too, is generally present to a greater or less degree. Pyonephrosis, which may at times give rise to a large renal tumour, is a complication, and one which calls for surgical interference. A perinephritic abscess may follow the bursting of a pyonephrosis, or may occur without this antecedent. It is met

with now and again. Haematuria is not an infrequent complication. Microscopically red blood cells are commonly present; but macroscopic haematuria may occur at the onset of the disease or at some time during its course. It has been pointed out by some of the early writers that haematuria may be a sign of a simple ureteral obstruction, before infection has occurred; and this seems very possible as a history of haematuria in a previous pregnancy is now and again recorded. Once haematuria has occurred the blood must furnish a better medium for the growth of micro-organisms than does normal urine.

B. *Complications apart from the Urinary Tract.* In the early history of the illness it is common to find an account of uterine pains and some loss of blood by the vagina, followed shortly after by the typical picture which has been described. To this case also the remarks about the existence of a suitable medium for organisms may be applied; or it may be considered that the threatened miscarriage is an early complication and is due to toxaemia. Miscarriage or abortion is frequent; and this indeed seems to be the way in which nature terminates the disease if left to herself. Complications in the respiratory system are not rare. Pneumonia may be present when the case is first seen, or may occur later. Pleurisy is common enough on the side of the affected kidney; and in one case the fluid withdrawn from a right-sided pleural effusion grew a pure culture of the bacillus coli. The proximity of the kidney to the pleura explains this pleurisy without difficulty, especially if it be recollected that some swelling and redness in the loin is not infrequent. In this extension to the pleura we have an explanation of the cough which is a common symptom of the disease. Apart from definite signs of disease in the lung or pleura, it is common to find diminished breath-sounds on the affected side, and some fine loud crepitations. The feeble breath-sounds are explicable by the diminished movement of the side, and chiefly the diminished diaphragmatic movement, due to the pain suffered by the patient if she breathes freely. The hurried respiration, the cough, and the feeble air entry at the right base often lead the practitioner to a provisional diagnosis of pneumonia. Abscesses in the lungs and empyema may be met with, but this may only be a part of the pyaemia which sometimes occurs in the worst cases.

One case in my own list, which occurred during the puerperium, had all the features of a progressive endocarditis, so that it was difficult to say whether the kidney trouble was primary or secondary. Ruppaner also narrates a case where acute endocarditis was present as a complication.

It has been noted earlier that the toxaemia of pregnancy, leading to eclampsia, may coexist with pyelitis, and this should also be referred to here among the complications.

### *Diagnosis.*

Opitz aptly likens the diagnosis of Encyopyelitis to the diagnosis of a twin pregnancy. 'In most cases it is extremely easy, in others it is difficult, the latter especially when one is not thinking of the disease.' Some of the common

errors in diagnosis have already been mentioned incidentally. In the cases investigated the error of diagnosis has been noted where possible and a list of the common mistakes may now be given. In the *acute cases*, appendicitis is a common diagnosis; less frequently pneumonia, pleurisy, influenza, especially the gastro-intestinal form, or some other specific fever; and in those who have been in the tropics, malaria. Occasionally also gastritis is suspected, biliary colic, or some acute abdominal condition. In the *chronic cases*, tuberculosis is generally diagnosed, and the presence of a cough is likely to suggest this. In the *subacute cases*, enteric fever or progressive endocarditis may well be suspected. A common error, not included in the above list, but which makes it difficult to collect instances of the disease from hospital records, is to call the cases 'albuminuria of pregnancy'. Champetier de Ribes, in discussing Legueu's paper at the surgical congress held in Rouen, 1904, stated that since his attention had been drawn to the subject, he had discovered that many cases called albuminuria of pregnancy were no other than mild forms of pyelo-nephritis. The mistake is the more easily made as there may be much albumin in the urine of a case of pyelitis.

The chief points which aid us in the diagnosis of Encyopyelitis may be summarized as follows:—

(1) The irregular temperature.

(2) The pain. It is at first hypogastric or in the iliac fossa, later chiefly epigastric or in the posterior renal position.

(3) The results of examination. The renal tenderness is always present at some stage of the disease if a careful examination be made.

(4) The urine. This is usually acid and slightly cloudy; it contains pus and a varying quantity of albumin. In a chronic case, however, the urine may be normal when examined; and to test the urine but once is certainly useless if the result is negative.

The diagnosis from a simple cystitis requires special mention, and may be difficult in certain cases. The presence of vomiting, rigors, or kidney pain, are all enough to suggest a pyelitis if they occur in addition to the symptoms of cystitis; the three-glass test may also be tried. In any case it is better not to be satisfied with the diagnosis of cystitis in pregnancy when it is accompanied by an indefinite fever, but to put the patient to bed and watch her.

In the *puerperium* it may be hard to distinguish pyelitis from puerperal fever. It is nevertheless important to do so, as therapeutic measures may otherwise be directed to the uterus, and these are not to be desired while the vulva is bathed in a stream of bacteria at each micturition.

Wallich suggested that the relation of the pulse-rate to the temperature might be of assistance. He found that the rate did not rise in proportion to the temperature. He did not, however, speak of a large number of patients, and a careful consideration of the cases used in compiling this paper failed to reveal any definite relationship. Such special aids to diagnosis as the cystoscope or

urinary segregation should not be forgotten. Finally, it may be said that the old rule which is applicable to other diseases is the most valuable aid to the diagnosis of Encyopyelitis. Each case should be regarded as a fresh case, and examined as a fresh case every day until a definite diagnosis has been made.

### *Prognosis.*

The usual headings under which this is considered are:—(1) The mother; (2) The child.

#### (1) *The mother.*

Most authors regard the prognosis in the mother's case as very favourable. Vinay and Cade say that with suitable treatment the disease should not last more than ten days, and it is rarely serious enough to cause a miscarriage. Haeberlin says it is a terrifying disease but not serious; and the chief duty of the consultant is to reassure the patient's friends and her medical attendant. It is true that death seldom occurs as an immediate result of the disease; but the prognosis of early writers seems, none the less, far too favourable. It is impossible to estimate the death-rate merely from the cases recorded in the literature; and moreover it is uncertain how many cases die indirectly at a remote date. The first 13 cases which I saw personally, of which 4 died, give a death-rate of 30 %, but this is probably too high; on the other hand, the death-rate of 1·8 % in the cases collected from the literature is ridiculously low. It is perhaps an under estimate to say that the maternal mortality in Encyopyelitis, including immediate and remote cases, is 12–15 %; about the same as in enteric fever. A long-continued fever with extreme wasting may lead directly to death after delivery; or to death within a few years from phthisis, contracted while the patient's resistance was at its lowest. The occurrence of the chronic coli pyelitis that is discovered long after labour must also be borne in mind; calculi, also, may form later in the damaged kidney.

It would seem possible that chronic interstitial nephritis may occur indirectly in later years, as the result of Encyopyelitis; but the disease has not been long enough studied, nor the cases sufficiently followed, to justify any conclusion in this respect.

Apart from obstetrical treatment a number of patients come sooner or later to operation, perhaps 15 % to 20 %, and in 5 cases out of 206 it is recorded that nephrectomy was done after a previous nephrotomy.

As has been asserted, the discovery of the peccant organism does not help our prognosis much; but in cases where staphylococci are present surgical intervention will probably be necessary before the disease is cured. The same may be said of those cases which do not react favourably to urotropine.

#### (2) *The child.*

The prognosis for the foetus is grave indeed. In 131 cases 70 children were born at term, of whom 3 died soon after birth; in 61 there was abortion

or premature labour: of these, 21 were born alive. In few of these cases is the history of the child recorded after birth; in none is it recorded for longer than a month. It is probable that the above mortality is too low, for the children are often undersized and delicate even if born at term.

### *Treatment.*

This may be:—(*a*) Medical; (*b*) Obstetrical; (*c*) Surgical.

(*a*) *Medical treatment* is sufficient in the majority of cases. Frequently the horizontal position succeeds alone in curing the disease, probably by altering the relative position of uterus and ureter. The position is more effective if the foot of the bed is raised. The lateral decubitus has been found effective by many observers, and Sippel has shown conclusively that it does remove pressure from the ureter. In a pregnant patient with a persistent fistula after nephrotomy for Encyopyelitis he found that when she was lying on the opposite side to the fistula the discharge ceased; the fistula was ultimately induced to heal in this way.

Different therapeutic values have been attached by different writers to a strict milk diet. Most physicians order it. Ziegelmann states that a milk diet is indicated because it diminishes the virulence of the organisms in the intestine. This is possible in Encyopyelitis, but it is certainly not so in cases of epidemic diarrhoea, in which disease the virulence of the organisms in the intestine is greatly enhanced by milk. Plenty of fluid should be given in addition to the milk. Alkaline waters such as Contrexéville, Vichy, or Evian are usually preferred. The important point is to increase the flow of urine through the kidneys, and nothing is so effective for this as distilled water.

Of drugs, purgatives are necessary, without a doubt, and a number of cases seem to get well when treated merely by rest in bed and by aperients. The aperient used is not of great importance; calomel and the sulphates are among the best. Several drugs are used because they are believed to have some specific action in curing the disease. Salol has been extensively used; methylene blue is also recommended strongly by some writers, chief of which is Marteville, who obtained very successful results from its use. Aspirin is recommended by Ruppaner. The drug that has been more successful than any other in the cases that I have seen is hexamethylenetetramine, or, to use the name by which it is better known, urotropine. So many times has its administration been successful, even after several other drugs had been tried, that its value seems to be proved to the hilt in these cases of Encyopyelitis. Unless the case be a severe one, or unless complications exist which are beyond medical treatment, the temperature will fall within three days of the first administration of the drug. Others have obtained equally good results from it, and even Marteville, who strongly recommends methylene blue, says that urotropine was found successful in certain cases which did not get well under the other treatment. Five to ten grains of the drug, preferably the smaller dose,

may be given three times a day in half a pint of hot water. It is often prescribed with acid sodium phosphate in order that the urine may be rendered acid. It is, however, open to doubt whether the acid sodium phosphate of commerce has much influence on the urine: an alkaline urine is made acid with urotropine alone, while acid sodium phosphate without the urotropine has not this effect. Vomiting sometimes occurs under this treatment, and if a diminution of the dose or a further dilution does not prevent this, the urotropine as originally put on the market may be tried in place of the cheaper drug, hexamethylenetetramine. If vomiting still continues, urotropine may be stopped and helmitol substituted for it in the same doses.

Local treatment, such as poultices and opium or belladonna fomentations, is not to be despised, as it frequently relieves pain and allows sleep.

(*b*) *Obstetrical treatment.* As far as it is possible to lay down rules in such a matter the following may be given. Induction of labour is to be advised—

(1) In cases of bilateral Encyopyelitis.

(2) In cases of relapse where the illness breaks out for a second time in a pregnancy.

(3) If it occurs again in a second pregnancy after a prolonged attack in the first, or when there have been recurrences in the interval between the pregnancies.

(4) In the first attack if the disease resists treatment by urotropine, rest and a fluid diet for more than fourteen days.

(*c*) *Surgical treatment.* The treatment may be directed to the bladder, which may be washed out or, as Pasteau suggests, intermittently distended; or operations on the kidney may be performed, such as nephrotomy or nephrectomy. In Encyopyelitis it seems clear that nephrectomy should be avoided if possible, as nephrotomy is generally successful. Moreover, if after nephrotomy the patient becomes pregnant again, she may be attacked with pyelitis in the remaining kidney, as in Lennander's case, and this is a serious matter.

In conclusion, I have to thank Dr. Maxwell, the Obstetric Tutor at the London Hospital, for valuable suggestions and for advice on the literature; and Dr. Simey, late Medical Registrar at the London Hospital, for help with the investigation of cases; to him I am indebted also for the word which was coined for the first page of this paper, Encyopyelitis.

*Conclusions.*

(1) That Encyopyelitis is commoner than is usually thought. Every practitioner in the course of a lifetime will meet with a few cases. More attention should therefore be paid to this disease in the Medical Schools.

(2) That the disease is due to an infection of the kidney pelvis with organisms, usually with bacillus coli communis, and that these organisms usually follow an ascending course. A similar infection can occur in women apart from pregnancy, and even in men.

(3) That the prognosis, both immediate and remote, is worse than has been hitherto supposed.

(4) That the treatment should be medicinal, by the internal administration of urotropine; and if this does not succeed, recourse should be had to the induction of labour without undue delay. Nephrotomy should never be performed until the obstetrical treatment has failed and the patient is still ill after the puerperium. Nephrectomy is only justifiable in rare cases as a cure for a persistent fistula or when the kidney is completely disorganized.

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CRITICAL REVIEW

# POLYCYTHAEMIA, ERYTHROCYTOSIS AND ERYTHRAEMIA

By F. PARKES WEBER

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## PART I. POLYCYTHAEMIA.

*Definition, &c.* Polycythaemia or Polycythaemia rubra (French 'Polyglobulie') signifies a condition of the blood in which the number of the red corpuscles (erythrocytes) is decidedly above the average.

Slight physiological variations are connected with age, sex, and normal discharges (prolonged sweating, &c.) and probably also with atmospheric temperature; and greater physiological variations are connected with atmospheric pressure (living in high altitudes). In ordinary low altitudes the standard number of red cells in a cubic millimetre of human blood is taken as 5,000,000 for healthy males after the 'polycythaemia neonatorum' of the first few days of extra-uterine life has passed off. For women the average is slightly less than for men.

The purpose of the present article is chiefly to consider the form of polycythaemia known as 'erythraemia', but in order to limit and define the group of cases to which this term can be applied it will be necessary first of all to classify the other forms of polycythaemia and shortly to discuss the various conditions which are known (or may be supposed) to be capable of giving rise to polycythaemia.

### Relative and absolute (true) Polycythaemia.

Polycythaemia may be (*a*) relative or (*b*) absolute (true).

(*a*) Mere *relative polycythaemia* is due to concentration of the blood, such as may be caused by choleraic diarrhoea or other excessive fluid discharges from the body (copious sweating). It is doubtless almost always of only temporary occurrence (possible exceptions occur in some cases of recurring night-sweats, &c.), and the diminution in volume of the blood-plasma, which causes it, is quickly recovered from when the normal osmotic conditions are re-established. Some degree of local relative polycythaemia can be induced (experimentally, as Cohnheim long ago showed, or by disease) in one limb or in one part of the body by obstruction to the return of venous blood from the

part in question; the explanation of this is that the delay of the blood-flow allows longer time for lymph to leave the blood-vessels, and so gives rise to local blood-concentration. As, however, will be afterwards pointed out, a condition of blood-stasis (impeded circulation) affecting a large portion of the body may probably sometimes give rise to a secondary (general) absolute polycythaemia as well as more directly to a (local) relative polycythaemia.

(*b*) In *absolute* or *true polycythaemia* (polycythaemia rubra vera) the total number of red corpuscles in the body is increased, and there is evidence, to which we shall later on refer, which shows that in most, if not in all, cases of absolute polycythaemia the total volume of blood in the body is increased as well as the number of corpuscles. It is quite probable that in certain patients with cardiac valvular defects, &c., a condition of absolute polycythaemia exists unaccompanied (owing to simultaneous relatively greater increase in the total volume of blood) by relative polycythaemia, but for our present purposes we need consider only those cases in which the presence of absolute polycythaemia is evidenced by the persistence of a relative polycythaemia discovered on making a blood-count in the ordinary way.

The possibility of cases of absolute polycythaemia being regarded as cases of mere relative polycythaemia (i. e. mere blood-concentration) is unlikely for the following reasons:—

(1) The absence of the recognized causes (diarrhoea, excessive sweating, &c.) of diminution in the total quantity of blood.

(2) The plethoric (full-blooded) or congested appearance of some of the patients.

(3) The persistence of the polycythaemia (merely relative polycythaemia, as already stated, is almost always only temporary).

(4) In some cases, moreover, as we shall subsequently point out, the total quantity of blood in the body can be estimated and proved to be in excess of the average.

In distinguishing cases of erythraemia from other forms of polycythaemia it is mainly or solely with the various classes of absolute polycythaemia that we are concerned.

### Primary and secondary Hyperplasias of the Blood: Erythraemia and Erythrocytosis.

By analogy with cases of leukaemia and leucocytosis, cases of absolute polycythaemia have been divided into two main divisions:—(*a*) apparently primary cases of hyperplasia of the red cells, i. e. cases of erythraemia; and (*b*) secondary or symptomatic cases of hyperplasia of the red cells, i. e. cases of erythrocytosis.

In this way the term 'erythraemia', as proposed by W. Türk, H. Hirschfeld and W. Osler, is reserved for cases in which the increase in the number of red cells, or rather the excessive erythropoiesis of which the polycythaemia is the

expression, appears, as far as our present knowledge goes, to be the primary disorder, just as in leukaemia the increased formation of white cells appears to be the primary disorder. On the other hand the word 'erythrocytosis', as suggested by Hirschfeld, is applied to cases in which the polycythaemia is secondary and in which it generally appears to represent a conservative vital reaction, i. e. an effort on the part of the organism to compensate for some difficulty in the oxygenation of the blood and tissues of the body. Erythrocytosis is thus analogous to leucocytosis in the more recent sense of the latter term, namely as signifying a secondary or symptomatic (generally a reactive or conservative) increase of the white corpuscles, such as may result from streptococcal or other microbic invasions of the body.[1] Thus, in all cases of erythrocytosis there is as much cause for the hyperplasia of the red blood-corpuscles to occur as in cases of renal or valvular disease there is for the heart to become hypertrophied.

The best known forms of erythrocytosis are those connected with residence at high altitudes and diminished oxygen-tension in the inspired air and those due to imperfect oxygenation of the blood and tissues owing to circulatory disturbance in chronic cardiac and pulmonary complaints, especially cases of congenital stenosis of the pulmonary orifice of the heart.

### The causes of Polycythaemia in cases of Erythrocytosis and in cases of Erythraemia.

In regard to the polycythaemia of chronic cardiac and pulmonary diseases there can now be no doubt that imperfect oxygenation of the blood and tissues is the exciting cause of the polycythaemia, in fact that deficiency of oxygen, as was many years ago suggested, stimulates the functions of the red bone-marrow so as to cause an increased formation of red cells. According to this view the polycythaemia is a 'conservative' or 'compensatory' vital reaction on the part of the individual, an automatic attempt to make up for deficient oxygenation of the tissues by increase in the number of the red blood-cells, which are the oxygen-carriers of the blood. Post-mortem examinations in cases of chronic cyanosis of cardiac or pulmonary origin help to confirm this hypothesis, for, in such cases, although the red colour of the bone-marrow of the shafts of the long bones is partly due, as I have satisfied myself, merely to engorgement with blood, evidence of abnormal haemopoietic activity is likewise obtained. It is surprising that in this respect very few exact observations have as yet been recorded, but E. Weil (1901), in post-mortem examinations on two children with congenital stenosis of the pulmonary orifice of the heart and chronic cyanosis, found that there was red transformation of the bone-marrow, microscopic sections

[1] It must, however, be remembered that the word 'leucocytosis' is still sometimes employed to signify a moderate increase in the number of white blood-cells, whether reactive in nature (constituting a 'leucocytosis' in the modern sense of the term) or arising as an early stage of leukaemia (the so-called 'leucocytic stage of leukaemia').

of which showed that all traces of the normal fatty tissue had disappeared. L. G. J. Mackey (1907) examined microscopic sections made by James Miller from the bone-marrow of a case similar to those of Weil and was able to confirm Weil's results. In a case of chronic cyanosis from pulmonary emphysema but without polycythaemia Mackey found the bone-marrow normal.

The polycythaemia of high altitudes,[2] which is now at last universally allowed to be an absolute or true polycythaemia, must be explained in the same way, as indeed F. Miescher suggested in 1893. It represents, in fact, a conservative vital reaction on the part of the individual (that is to say on the part of his bone-marrow) to compensate for the diminished oxygen-tension in the inspired air at high altitudes, i. e. to compensate for the resulting difficulty in maintaining proper oxygenation of the blood and tissues of the body. Animals when kept at high altitudes react by a polycythaemia just as men do, and the bone-marrow of dogs which have developed a polycythaemia from being kept at high altitudes, has been carefully, macroscopically and microscopically, examined and found to give abundant evidence of increased erythropoietic activity (Zuntz, Loewy, Mueller and Caspari). Jaquet and Suter's observations on the increase of blood-corpuscles and haemoglobin in rabbits when kept at Davos, the famous Swiss mountain resort, are well known, and will be referred to again later on. These observers found that the increase in red cells and haemoglobin was very striking. Jaquet obtained quite similar results (nearly parallel increase in the figures) by keeping rabbits in chambers, in which the atmospheric pressure was artificially reduced to correspond to a fall of 100 mm. in the height of the barometric column, which is equivalent to a rise of over 1,000 metres in altitude. Paul Regnard had already maintained that in animals an artificial atmosphere containing excess of oxygen reduced the number of red cells in the blood, and he had also increased the haemoglobin value of the blood by subjecting animals to an artificially rarefied atmosphere. But the value of his results was called in question owing to the artificial conditions to which the animals were subjected and the possibility of excess of carbonic acid playing a part in the latter experiment. Sellier (of Bordeaux) had likewise shown in 1895 that experimental reduction of the oxygen-tension in the air was sufficient to induce a polycythaemia in animals. Similar experiments had also been carried out by O. Schaumann and E. Rosenquist on dogs, rabbits, and pigeons. They were kept in an artificially extremely rarefied atmosphere, corresponding to an altitude of about 4,000 metres, and by this means not only were the red cells (erythrocytes)

[2] The extensive literature on this subject commences with Paul Bert's observation in 1882 that the blood of the Peruvian mountain-sheep (Llama), was capable of absorbing much more oxygen than the blood of sheep living at low elevations. Then follow the writings of A. Muentz (1890), F. Viault (1890), F. Miescher (1893), F. Egger, A. Mercier, A. Jaquet, F. Suter, Campbell and Hoagland, Abderhalden, Armand Delille and Mayer, Buckmaster, Schaumann and Rosenquist, P. Regnard and many other investigators. For an account of all this literature see the elaborate work on the effects of high altitudes by Zuntz, Loewy, Mueller and Caspari (1906), Jaquet's (1904) and Buckmaster's (1906) monographs, and the short summary in H. and F. P. Weber's *Climatotherapy* (London, 3rd edition, 1907, pp. 60–2).

increased in number, but in the case of the dogs and rabbits nucleated red cells (erythroblasts), that is to say, young unripe forms of red cells, were made to enter the circulating blood from their normal home in the bone-marrow. Various observations quoted by Jaquet and others show that the changes in the quality and quantity of the blood which occur as the result of living at high altitudes and which can be experimentally produced by subjecting animals to an artificially rarefied atmosphere, cannot be explained as the effects of low temperature or increased light. As further confirmation of these views it may be noted that E. Kuhn by the use of his so-called 'suction-mask', that is to say by periodical artificial diminution of the oxygen-pressure in the lungs, has apparently been able in some persons to produce a decided increase of red cells in the blood.

Here we may mention a number of other (clinical or experimental) conditions, which by interfering with the proper oxygenation of the blood and tissues of the body, may give rise to a secondary polycythaemia (erythrocytosis), viz.:—Experimental stenosis of the superior and inferior venae cavae and artificial compression of the thorax (Reckseh); diminution of oxygen and increase of carbonic acid gas in the inspired air (Sellier, Palleri and Mergari); clinical or experimental stenosis of the trachea or larynx (Vaquez, Sellier, Labbé, Quiserne); clinical or experimental pneumothorax (Raybaud, Schlosser, Auscher and Lapicque).

In regard to the cause of the polycythaemia in cases of erythraemia nothing certain is at present known, excepting that, as the changes found in the marrow of the shafts of the long bones at necropsies and in one instance (G. A. Gibson) during life (i.e. for 'biopsy' purposes) have shown, it is brought about by increased activity in the erythropoietic functions of the bone-marrow. But an increased activity of the bone-marrow is doubtless also the immediate cause of the other classes of absolute polycythaemia, as I have already pointed out in regard to the polycythaemias dependent on chronic cardiac and pulmonary diseases, and on residence at high altitudes. There is no evidence that increased durability of the red corpuscles and increased resistance towards haemolytic agents plays any essential part in the causation of any kind of polycythaemia, but I shall have to return to this subject later on.

I think I have now sufficiently explained what appears to be the only tenable view in the present state of our knowledge regarding the origin of the various classes of absolute polycythaemia. In all cases the polycythaemia is due to an increased haemopoietic (especially erythropoietic or 'erythroblastic') activity of the bone-marrow, that is to say it is always myelogenous in origin; but although the exciting cause of this increased functional activity is recognized, as I have already explained, in regard to the secondary polycythaemia (erythrocytosis) connected with disorders of the circulatory system and residence at high altitudes, it remains unknown in regard to the 'myelopathic polycythaemia' or 'erythraemia'. In this last class of polycythaemia the excessive functional activity of the bone-marrow constitutes as yet the primary recognizable morbid factor, and that is the reason why, in 1905, I proposed the term 'myelopathic' (not merely myelogenous or myelogenic) polycythaemia for it.

The excessive formation of red blood-corpuscles in myelopathic polycythaemia may perhaps, as has already been mentioned, be regarded as analogous to the excessive formation of white blood-corpuscles in cases of leukaemia. It can likewise be explained as the result of a morphological and functional reversion to (or, in certain cases, persistence of) a past condition (normal in foetal life and early life after birth) in which the bone-marrow of the shafts of the long bones is red and still actively engaged in the formation of erythrocytes, instead of being yellow and fatty as most of it is in healthy adults. If the analogy to leukaemia proves to be appropriate, the term 'erythraemia' must be considered preferable to the term 'myelopathic polycythaemia' and the various other names which have been proposed, since it implies that the disease is one which in regard to erythrocyte-formation is analogous to leukaemia in regard to leucocyte-formation. In fact, if, as H. Ribbert believes, there is a form of 'myeloma' (that is to say of growth originating in the elements of the bone-marrow) which should be termed 'erythroblastoma', because the tumour-cells are related to erythroblasts, it seems possible that cases of erythraemia may bear a relation to cases of erythroblastoma similar to that which cases of leukaemia bear to cases of leucoblastic myeloma. It must, however, be remembered that Ribbert's case of 'erythroblastoma' is as yet the only one recorded and the existence of so remarkable a kind of tumour-formation certainly needs confirmation.

Objections to the view that the excessive formation of red cells in the bone-marrow is the primary pathological condition in erythraemia have been urged by F. Lommel, J. Bence and others; and it must be admitted that in several cases of clinically (that is presenting the clinical symptom-complex of) splenomegalic polycythaemia evidence of general or local blood-stasis (impeded circulation) has been ascertained, suggesting that the polycythaemia, at all events in the cases in question, was more or less reactive in nature and secondary to imperfect oxygenation in the whole or part of the body. According to Bence, the polycythaemia of splenomegalic polycythaemia can be diminished by oxygen-inhalation, just as he claims that the polycythaemia of cardiac origin and that due to high altitudes can be, but R. Stern and others obtained negative results by this method. I shall return to these subjects in the later portion of this article devoted to erythraemia.

### Characters of the Blood and Blood-forming Tissues in absolute Polycythaemia.

Before proceeding further it will be well to consider certain features common to erythraemia and erythrocytosis. We have already given our reasons for believing that in all cases the *essential change in the blood-forming tissues is an increase in the erythroblastic elements of the bone-marrow.* We have now to consider *certain characters of the blood probably common to all classes of absolute polycythaemia.*

*The degree of relative polycythaemia in cases of absolute polycythaemia.* In all classes of absolute polycythaemia, but especially in erythraemia, the increase in the number of red cells is sometimes very remarkable. In cases of congenital heart disease, with more or less chronic cyanosis, blood-counts of seven to eight million red cells to the cubic millimetre are not at all unusual, as in the case of a girl, aged seventeen years, whom I showed at the Clinical Society of London in 1907, and whose red corpuscles had varied from 6,375,000 to 7,352,000 in the cubic millimetre. Many much higher counts are referred to by Quiserne. Some authors formerly thought that in chronic cyanosis connected with heart disease the red corpuscles never exceeded eight millions per cubic millimetre of blood, but in congenital pulmonary stenosis and more complicated forms of congenital heart disease the following counts prove the contrary:—9,447,000 (Banholzer, 1894); 8,470,000 (G. A. Gibson, 1895); 10,540,000 (Variot, 1897); 9,860,000 (Audry, 1902); 9,084,000 (Babonneix, 1902); 9,800,000 (Fromherz, 1903); over 10,000,000 (Friedel Pick, 1904, and J. H. Drysdale, 1905); 8,320,000 (Batty Shaw, 1907). In a child aged two months with congenital heart disease, in which a subsequent necropsy showed also that the spleen was congenitally absent, Gardère (1908) found the red blood-cells 9,000,000, and the white cells (chiefly mononuclear forms) 25,000. Recently at the Clinical Section of the Royal Society of Medicine (November 8, 1907), Murray Leslie showed a woman aged 22 years with congenital heart disease, who had cyanosis and clubbing of the fingers from birth, and whose blood was found to contain over 11,000,000 red cells to the cubic millimetre; and even this is not the highest count recorded in congenital heart disease.

In three patients at the German Hospital, London, with cyanosis connected with chronic pulmonary emphysema and circulatory insufficiency, we obtained blood-counts of respectively 6,350,000, 6,850,000, and 6,870,000 red cells per cubic millimetre, and in a fourth case the counts on various occasions were 6,930,000, 8,230,000, and 9,357,000.

In normal persons the 'polycythaemia of high altitudes' (including that of residence at localities 6,000 feet and more above sea-level) may reach seven to eight million red cells per cubic millimetre of blood.

In cases of erythraemia counts of nine to ten million red cells and over have been fairly common, with haemoglobin-values up to 160 to 180 per cent. of the normal standard, and even higher. If samples of such extremely polycythaemic blood (in which coagulation has been prevented by the addition of citrate or tartrate of potassium) are allowed to stand in a cylindrical glass vessel until the corpuscles have had time to settle down, it will be found that the corpuscular sediment occupies over nine-tenths of the whole column, the blood-plasma forming only a thin layer on the surface; whereas in normal human blood the corpuscular layer and the layer of blood-plasma are about equal in volume. It has indeed been supposed that there is not 'standing room' for more than about 13,000,000 red cells to the cubic millimetre, as R. Hutchison has expressed it. In cases of polycythaemia with cyanosis and splenomegaly

blood-counts of 12,000,000 have been registered by Cabot, 12,500,000 by Reckzeh, and 13,600,000 by Koester, whilst haemoglobin-values of 190 to 200 per cent. (Sahli's methods) have been recorded by both Rosengart and Koester. The latter states that the haemoglobin value (estimated by Sahli's apparatus) in his case was on one occasion 240 per cent. (misprint ?) of the normal. In haemoglobin measurements there are, however, greater sources of error than in blood-counts.

The degree of polycythaemia may of course vary to some extent according to the part from which the blood is taken, as Malassez long ago insisted. Obstruction to the return of blood from a limb increases the proportion of corpuscles in the affected part (local relative polycythaemia), as Cohnheim proved experimentally in animals; and vasomotor influences (constriction or dilatation of vessels) affect the relative erythrocyte-count by altering the local concentration of the blood, as experiments by Grawitz, Cohnstein and Zuntz, and Chéron have shown. In a patient whose case was recorded by Reckzeh (his third case), in whom there was progressive obstruction to the blood-flow in the superior vena cava, the cyanosis and polycythaemia were for a long time limited to the portion of the body chiefly affected by this obstruction.

Though the blood used for blood-counts is practically always capillary blood it must not be forgotten that in polycythaemia the increase of red cells is generally not quite uniform in the arteries, capillaries and veins, at all events when the polycythaemia is secondary to impeded circulation. Thus G. A. Gibson on one occasion in a boy, aged 16 years, supposed to be suffering from mediastinal pericarditis, found the erythrocytes in the arterial blood to be 7,000,000, in the capillary blood 8,500,000, and in the blood from a vein 10,000,000. Palleri and Mergari in a case of congenital pulmonary stenosis counted the red cells in capillary blood from the finger at 6,650,000, in venous blood from a vein in the arm at 6,400,000, and in arterial blood from the temporal artery at 5,950,000. Ascoli, however, in a case of (clinically) splenomegalic polycythaemia made the erythrocyte-count from the radial artery 6,100,000 when the capillary blood from the lobe of the ear only gave 6,000,000 (? admixture of serum from the subcutaneous tissue). Geisböck in 'hypertonica polycythaemia' found almost the same number of cells in arterial as in venous blood. On one occasion in one of his patients with high blood-pressure the red corpuscles were counted in blood from the radial artery, in capillary blood from the finger, and in venous blood from the median vein; and the resulting figures were respectively 10,530,000, 10,695,000, and 10,775,000.

*The viscosity of the blood in polycythaemia and its relation to the blood-pressure.* The blood-viscosity is always raised when the number of red corpuscles per cubic millimetre is much increased. This can be demonstrated, as I have myself found, in specimens of blood from patients with polycythaemia and chronic cyanosis of cardiac or pulmonary origin. So also in two cases of splenomegalic polycythaemia I found the viscosity of citrated specimens of the venesection-blood to be more than twice the normal. Supposing the viscosity

of normal human blood to be about 5·1 to 5·3, that is to say 5·1 to 5·3 times that of water (when the temperature of both is 38° C.), Lommel found the viscosity to be over 11·0 in two cases of polycythaemia with splenomegaly (in one patient the splenomegaly was only temporary), whilst Bence in another case obtained figures varying from 15·9 to 20·9, and Münzer in another case showed that the figures varied between 12·0 and 23·0, partly according to the special form of viscosimeter which he employed; in Löw and Popper's first case the viscosity of the citrated blood (by Hirsch and Beck's method) was 10·4; in Saundby's case of 1907, J. H. Watson (by Denning and Watson's method) estimated the viscosity at 9·4. In three cases of cyanosis in heart disease, and in one case of bronchitis with emphysema, Bence obtained viscosity-values of between 6·9 and 8·2. Determann has shown that the viscosity of the blood is increased, like the number of erythrocytes is, at high altitudes. In some rough experiments made in 1904 with J. H. Watson on citrated horse's blood, we showed that the variations in viscosity generally depended mainly, though of course not entirely, on the proportion of the blood-corpuscles to the volume of blood-plasma. It was found, for instance, that horse's blood-plasma, artificially mixed with two millions of red corpuscles to the cubic millimetre, took 84 seconds to pass through the bulb of the 'viscosity-tube', whilst a sample containing four million red corpuscles to the cubic millimetre took 110 seconds to pass through the bulb of the same tube. All observers who have investigated the subject have found that increase in the number of red corpuscles raises the viscosity of the blood, but we may especially refer to the early work of A. Czerny (1894), the experiments of C. Jacob (1901), and Sherrington and R. J. Ewart (1904), and the elaborate papers on the subject by Determann (1906) and Denning and Watson (1906). On the whole subject of human blood viscosity we would refer also to the writings of Burton-Opitz (1900), Trommsdorff (1900), Hirsch and Beck (1901), J. Bence (1906) and W. Hess (1907).

In spite of the excessive viscosity of the blood, the blood-pressure in polycythaemia, though usually, is not always high, and in most cases the left ventricle of the heart is not greatly hypertrophied. Evidently the difficulty in circulation caused by the abnormal blood-viscosity is to a great extent avoided by compensatory dilatation of blood-vessels. This is just what some of the experimental work on the relation of artifically increased blood-viscosity to blood-pressure (Jacobj) would lead one to expect, but all observers are agreed that artificial increase of blood-viscosity does tend to raise the blood-pressure in spite of compensatory dilatation of blood-vessels.

*The haemoglobin-value of the blood in absolute polycythaemia.* The haemoglobin-value may be very greatly raised, but it is seldom increased to the extent corresponding to the increase in the number of red cells. Thus generally the colour-index of the red cells is below 1·0. It seems probable that the red cells may in some cases be numerically increased as a kind of compensatory reaction to make up for their deficiency in haemoglobin. Thus in some cases of syphilis, &c., a secondary polycythaemia (erythrocytosis) seems to be associated

with a subnormal haemoglobin-value, constituting a blood-state which may perhaps be termed a 'polycythaemic anaemia'.

*The specific gravity of the blood and blood-serum in absolute polycythaemia.* The specific gravity of the blood seems usually to be raised, but apparently often not in proportion to the degree of polycythaemia. The specific gravity of the blood-serum, however, is probably never raised when the polycythaemia is absolute. In erythraemia Weintraud found it below normal. According to Askanazy the specific gravity of blood-serum is normally 1028–1032. Weintraud found it only 1025–1026 in two of his erythraemia cases and Geisböck in one of his patients with 'polycythaemia hypertonica' made it 1025–1028.

*The dry residue of the blood and blood-serum in absolute polycythaemia.* The percentage in normal blood-serum is said to be 9·21 to 10·50. In two of Weintraud's cases of splenomegalic polycythaemia it was found to be 9·30 and 9·28 respectively, whilst in a similar case Senator gives it as 10·72. In a case of 'polycythaemia hypertonica' Mohr found it 10·1, and Geisböck in one of his best marked examples of the same condition made it 9·0 to 9·9. The estimation of the dry residue and specific gravity of the blood-serum in polycythaemic patients is of course of some value in excluding the possibility of blood-concentration. (I do not know that this point has been investigated in regard to the erythrocytosis of high altitudes in human beings.) The percentage of dry residue in the blood as a whole is doubtless rather above than below the normal in all forms of polycythaemia. In three erythraemia cases Weintraud obtained figures between 22·6 and 29·0 per cent., and in similar cases Senator found the percentage 27·2, and Löw and Popper 27·3, whilst Askanazy estimated the percentage in normal men as 20·3 to 22·8.

*Iron and albumen in the blood of absolute polycythaemia.* The amount of iron is probably raised in proportion to the increase in haemoglobin. In regard to the percentage of albumen in the blood-serum it is worth mentioning that both Weintraud and Senator found it in erythraemia cases decidedly below the normal (8·8 per cent. according to von Jaksch) for healthy adults; in one such case Weintraud also estimated the percentage of albumen in the blood as a whole and found it slightly below the normal (22·6 per cent. according to von Jaksch).

*The coagulability of the blood in polycythaemia.* The blood-coagulability appears to vary independently of the richness of the blood in red cells and haemoglobin. It may be raised or lowered in polycythaemia just as it may be in oligocythaemia.

*Increased haemolysis in absolute polycythaemia.* As the rate of production of the red cells in these cases is increased it may be concluded that the rate of their destruction is likewise probably increased, unless the cells are unduly resistant to haemolysis or otherwise peculiarly durable so as to have an abnormally long life. For this latter supposition there is certainly no evidence, although Fick (quoted by G. Schroeder) at one time was inclined to explain the 'polycythaemia of high altitudes' as due to a hypothetical increase in the

life-duration of the red cells. In two cases of erythraemia (Parkes Weber, Saundby) the resistance of the red cells to haemolysis (methods employed by Wright or Ribierre) was found to be about normal, and in one case (Vaquez and Laubry) it was found to be unduly low; these observations are opposed to any theory of increased durability of the red cells. Abeles in two cases of polycythaemia found the excretion of iron in the urine to be above the normal, an observation which as far as it goes supports the view that increased haemolysis accompanies absolute polycythaemia. In this connexion it may be added for what it is worth that the total excretion of urobilin has been estimated in three or four cases of (clinically) splenomegalic polycythaemia; in a case reported by Lommel it was found to be above the average and in Senator's two cases it was about normal, whilst Löw and Popper in their first case found it slightly raised. Evidence by microscopic examination after death regarding the amount of phagocytosis in the spleen in absolute polycythaemia is very scanty. In one case of erythraemia in which the spleen was microscopically examined H. Hirschfeld found very many cell-containing phagocytes present, but in another case he found very few. Owing, however, to the large size of the spleen in Hirschfeld's two cases it seems probable that in at least one of them the total phagocytosis of red cells was very greatly increased.

*The total blood-volume in absolute polycythaemia.* It is probable, as I have already mentioned, that in absolute polycythaemia the total volume of blood in the body is generally, if not always, above rather than below the normal average, that is to say the quantity which should correspond to the body-weight. In 1900 J. S. Haldane and Lorrain Smith published their 'carbon-monoxide method' of estimating the total volume of blood in the body, a method which made it clinically possible to recognize the presence of true plethora, and in 1906 C. G. Douglas tested this method in animals and found that the results obtained by it agreed fairly closely with those obtained by the old Welcker's method in which the blood had to be extracted from the tissues after the death of the animal. Oerum of Copenhagen, in a recent account of Haldane's carbon-monoxide method, points out that the importance of ascertaining the total blood-volume when examining the blood is something like that of estimating the total daily output when examining the urine. The carbon-monoxide method has been already employed in various cases of true polycythaemia in man. Lorrain Smith and H. L. McKisack, in the case of a boy, aged 12 years, suffering from adherent pericardium and chronic cyanosis, not only showed that the proportion of red cells to blood-plasma was excessive (relative polycythaemia), but also demonstrated by the carbon-monoxide method that the total volume of blood was far beyond the normal standard, so that there was undoubtedly a condition of true plethora present. The number of red cells in the cubic millimetre of blood was 6,340,000, and by the carbon-monoxide method it was ascertained that the total volume of blood in this boy's body was nearly double that of the normal standard. In the case of splenomegalic polycythaemia which I described in 1905, the total volume of the patient's

blood was estimated in the same way by Haldane himself, and was found to be greatly in excess of the normal. In fact, with a blood-count of between eight and nine million red cells to the cubic millimetre, and with a haemoglobin-value of about 150 per cent. of the normal standard, there was likewise a great excess of the total blood-volume, that is to say, a condition of true plethora was also present. This is exactly what one would suppose from the plethoric look of such patients and from the engorged state of their visceral blood-vessels as revealed at the few post-mortem examinations which have as yet been recorded. I have Dr. T. D. Acland's permission to state that in an as yet unpublished case of splenomegalic polycythaemia under his care at St. Thomas's Hospital, Dr. Haldane made a clinical estimation of the total blood-volume by the carbon-monoxide method, and showed that it was about two and a half times the normal. Dr. R. Hutchison also kindly informs me that in two typical cases of splenomegalic polycythaemia (accounts of which have not yet been published) at the London Hospital Dr. A. E. Boycott determined the total blood-volume by Haldane and Lorrain Smith's method and found it in both cases very much increased; in one of the two cases, indeed, it appeared to reach the extraordinary figure of 10,750 cubic centimetres, that is to say, probably more than three times the volume normally corresponding to the patient's body-weight. Quite recently, in another patient, Boycott and Douglas determined the total blood-volume by the same method and again found it greatly increased, as it was in all the other cases.

In regard to the polycythaemia of high altitudes there is less evidence of associated polyaemia (true plethora) in human beings, but Jaquet and Suter found that in rabbits kept at high altitudes (Davos) a very striking increase occurred, not only in the number of red corpuscles and richness in haemoglobin per cubic millimetre of blood, but likewise in the total quantity of blood (and haemoglobin) which could be extracted from the body. Guillemard and Moog, from their observations on rabbits at the summit of Mont Blanc, also conclude that the total blood-volume is increased at high altitudes.

*The relation of increased total blood-volume (polyaemia, plethora vera) to absolute polycythaemia.* Not many years ago the possibility of the persistence of a condition of plethora was denied by most authorities. R. von Limbeck, in the second edition (published in Germany in 1896, English translation, 1901) of his *Clinical Pathology of the Blood*, wrote: 'The doctrine of plethora, formerly a dogma, has received its death-blow, owing to the growth of experimental investigation. It was especially due to the works of von Lesser, Worm-Müller, and Cohnheim that the possibility of the persistence of a condition of plethora came to be denied.' In 1900, J. Lorrain Smith, by the 'carbon-monoxide method' previously referred to, proved that in the so-called anaemia of chlorosis the total volume of the blood was in reality greatly increased (in proportion to the severity of the disease), and now, as we have already pointed out, it appears that true (absolute and persistent) polycythaemia is always, or almost always, accompanied by a condition of true plethora (polyaemia).

Are there any experimental observations which throw light on this association of true plethora with polycythaemia? Yes, I think there are some, and, curiously enough, they are the very experiments of Worm-Müller (1875) on which Cohnheim based his assertion that plethora could not exist. These experiments and those of von Lesser (1874) did, indeed, prove the impossibility of suddenly producing a persistent plethora by the experimental transfusion method, but, at the same time, they wonderfully well illustrate the manner in which a condition of persistent polycythaemic plethora may arise under certain pathological (chronic cardiac disease, &c.) or physiological (residence at high altitudes) conditions. I shall, therefore, shortly describe the experiments in question as given in von Limbeck's work already referred to. When von Lesser and Worm-Müller tried to produce plethora artificially by transfusion of blood into an animal, the blood-vessels were at first enlarged to receive the excess and the blood-pressure was augmented, but a portion of the injected blood quickly began to leave the vessels, the lymph-stream increased, and the increase in the blood-volume gave place to an increase of blood-corpuscles (polycythaemia), which in its turn gradually disappeared. No bad symptoms were observed when the quantity of blood transfused amounted even up to approximately 80 or 100 per cent. of the (estimated) normal total blood-volume in the animal's body. Within half an hour after the transfusion half the injected fluid had already, according to Worm-Müller, left the blood-vessels, though the cellular elements remained, giving rise to a polycythaemia. In the case of a rabbit transfused for fifteen minutes from another rabbit, the red corpuscles counted before the experiment were 5,160,000 to the cubic millimetre, but twenty-two minutes after the transfusion they were 8,280,000 to the cubic millimetre. In these experiments the polycythaemia did not last long. Worm-Müller found that the number of corpuscles was reduced to the normal in two days. Similarly, in the case of a dog in which the quantity of the blood was much increased by transfusion, the number of red corpuscles in the cubic millimetre of blood was found to be greatly in excess thirty minutes after the experiment, but here again the polycythaemia was only transitory, disappearing some days after the transfusion, though of course less quickly than the artificial plethora did. From all these experiments it is clear that the circulatory system finds it much more easy to get rid of a superfluous quantity of blood-plasma than to free itself of a superfluous number of corpuscles, but why the 'plasma-plethora' in chlorotic patients is not got rid of remains a problem to be solved.

In no such experiments have the conditions prevailing in the various classes of polycythaemic polyaemia (plethoric polycythaemia) (plethora vera) of human beings been fulfilled. In all these cases in human beings the polycythaemia, as we have explained, arises from increased activity in the haemopoietic functions of the bone-marrow, and the increased activity of the bone-marrow is in its results practically equivalent to a gradual persistent transfusion of blood into the vessels. In other words, the bone-marrow in these cases is constantly

engaged in producing excess of blood,[3] and forcing all of it into the blood-stream. The increased total quantity, and polycythaemic quality, of the circulating blood are both therefore the natural result of the persistent increased formation of blood in the bone-marrow, and a similar condition of persistent polycythaemia would be obtained in Worm-Müller's experiments on animals, were it possible (which of course it is not) to modify his experiments so as to make the transfusion of blood a gradual persistent process, lasting, not for a few minutes, but for days, weeks, months, and years.

### Possible causes of Secondary Polycythaemia (Erythrocytosis) other than Chronic Cardiac and Pulmonary Diseases and Residence at High Altitudes.

We have already discussed erythrocytosis connected with residence at high altitudes (diminished oxygen-tension in the inspired air) and erythrocytosis due to imperfect oxygenation of the blood and tissues in chronic cardiac and pulmonary complaints. These probably afford the most typical examples of secondary polycythaemia, but we shall now have to consider other occasional causes of polycythaemia, because a case cannot be classed as one of erythraemia (primary absolute polycythaemia) until all adequate causes for secondary polycythaemia (and indeed relative polycythaemia) have as far as possible been excluded.

*Erythrocytosis secondary to blood-stasis (impeded circulation) not of cardiac or pulmonary origin.* Lommel and Reckzeh have especially urged the view that polycythaemia, and indeed polycythaemia with splenomegaly, though cardiac and pulmonary disease be absent, may, nevertheless, be secondary to impeded circulation, possibly more or less local in origin, for instance, extreme passive congestion in the portal system. In many cases presenting the symptom-complex of splenomegalic polycythaemia it must be admitted that evidence of more or less vascular obstruction has been found during life or at the necropsy, e.g. thrombotic changes in the spleen and other organs, cirrhosis or great engorgement of the liver, and disease of blood-vessels in the limbs. In two cases of polycythaemia with splenomegaly (van der Weyde and van Ijzeren's case and Lommel's first case) the necropsy showed that there had been chronic obstruction and final thrombosis in the portal vein. In those cases the polycythaemia may have been at all events partly due to the impeded circulation. Cases of polycythaemia with chronic cyanosis and splenomegaly may indeed be explained in this way when there is undoubted evidence of greatly impeded circulation and when there is likewise some adequate cause for the splenomegaly, but it must be remembered that chronic passive congestion of cardiac or cardio-pulmonary origin seldom gives rise by itself to clinically obvious

[3] It may be taken that the blood-plasma is in some way or other so dependent for its existence on the blood-corpuscles that the formation of blood-corpuscles in the bone-marrow is practically equivalent to the formation of blood.

splenomegaly; obvious splenomegaly is nearly always absent in cases of polycythaemia secondary to congenital or acquired cardiac disease.

*Polycythaemia and erythrocytosis of toxic origin.* Toxic conditions interfering with the proper oxygenation of the blood and tissues of the body sometimes give rise to a polycythaemia, probably to some extent reactive in nature, though doubtless often partly due to blood-concentration. The polycythaemia caused by acute phosphorus poisoning (Taussig, von Jaksch, R. Silbermann) only lasts for the first two or three days. Taussig, who was the first to discover its occurrence, counted 8,650,000 red cells to the cubic millimetre of blood in one case. According to Silbermann's statistics it is well marked in about 54 per cent. of all cases. More or less polycythaemia is frequently present in carbon-monoxide poisoning (von Jaksch, von Limbeck, G. Reinhold). Reinhold in one case found the red cells increased to 11,200,000 in the cubic millimetre, but a most striking feature in these cases is that in spite of the increase in the number of red cells the haemoglobin-value of the blood may be actually diminished, so that the condition may be termed one of 'polycythaemic anaemia'. Thus, in Reinhold's above-mentioned case, when the red corpuscles numbered over eleven million to the cubic millimetre, the haemoglobin-value of the blood (measured by Sahli's method) was only 90 per cent. of the normal, so that the colour-index of the red corpuscles was only 0·4, if we can rely on haemoglobin measurements in these cases of carbon-monoxide poisoning.

It is possible that the coal-tar derivatives, antipyrin, phenacetin, acetanilide (antifebrin), &c., which give rise to methaemoglobinaemia and cyanosis when taken in excess, may occasionally produce polycythaemia, though they usually cause oligocythaemia. Anyhow, the destruction of red cells in these cases is followed by a remarkable erythroblastic reaction, and in Stengel and White's case of chronic acetanilide poisoning with 'cyanotic anaemia' and splenomegaly the blood contained an extraordinary number of nucleated red cells. It seems that the haematoporphyrinuria of chronic sulphonal poisoning may sometimes be associated with a very decided increase in the number of red cells in the blood (see case of A. Fells in Appendix B.)

In regard to the artificial production of toxic oligocythaemias and toxic polycythaemias it appears certain that a toxin which in ordinary quantities will give rise to oligocythaemia may in some individuals, when given repeatedly in very minute doses, give rise to a polycythaemia. The explanation, in my opinion, is that in the former case the oligocythaemia is the expression of the (prevailing) 'action' of the toxin, and in the latter case the polycythaemia is the expression of the 'reaction' on the part of the organism being more powerful than the action of the toxin (cf. F. P. Weber, 'A Note on Action and Reaction in Pathology and Therapeutics,' *St. Bart.'s Hosp. Reports*, London, 1903, xxxix. 139).

As an exceptional and striking example of polycythaemia provoked by the direct 'action' of an 'agent' rather than as a 'reaction' towards it, we may

instance the work of Paul Carnot and Mlle. Cl. Deflandre on the effects of 'hemopoiétine' on the blood and bone-marrow. These observers found that an absolute polycythaemia could be artificially produced by the injection of serum from an animal in which an erythroblastic reaction was in progress. In one rabbit Carnot by this means was able to raise the number of red cells from 5,465,000 to 11,900,000 in the cubic millimetre of blood. After 14 days the count was still as high as 7,595,000. Comparison of the blood in the arteries, veins, and capillaries, and examination of the bone-marrow, left no doubt that the increase in the number of red cells produced by 'hemopoiétine' was an absolute increase, that is to say, not due to altered distribution of the corpuscles or to concentration of the blood, but to an increased production of red cells in the bone-marrow. On the other hand, as an example of polycythaemia provoked as a 'vital reaction' on the part of the organism towards a toxic agent, we may instance the results of Belonovsky, of St. Petersburg, who claims to have increased both the number of corpuscles and the amount of haemoglobin in the blood of anaemic persons by the injection of minute doses of haemolytic serum.

In this connexion a case recorded (1907) by Pel, of Amsterdam, is of great interest. In an officer, aged 66 years, suffering from attacks of paroxysmal haemoglobinuria, Pel found that there was decided polycythaemia (six to nine million red cells in the cubic millimetre of the patient's blood). It is very interesting also to know that J. McFadyean (1888) found a condition of great polycythaemia accompanying attacks of haemoglobinuria in horses. McFadyean (1893) stated that in horses an erythrocyte-count at the beginning of an attack might in some cases show nearly double the normal number of red cells. The blood-viscosity must therefore have been greatly raised. He suspected the presence of a dietetic factor in the aetiology of such cases, and we may call to mind that Burton-Opitz (1900) by means of a meat diet in dogs increased both the number of red blood corpuscles and the blood-viscosity.

It seems also reasonable to suppose that equal doses of a particular toxin when used in different individuals may give rise to oligocythaemia in some individuals and polycythaemia in others, according to their body-weight, age, and temporary state of reactive power. It is quite possible that there are various unknown toxaemias (of intestinal origin, &c.) which may sometimes cause oligocythaemia, sometimes polycythaemia and plethora.

*Erythrocytosis in Chronic Infectious Diseases.* An increase in the number of red corpuscles is sometimes met with in tuberculous, syphilitic, and probably also in old malarious cases, quite apart from the polycythaemia occasionally caused by great sweating, diarrhoeal discharge, &c. This increase in the red cells (like the more frequent diminution) is probably due to toxins circulating in the blood or to the local presence of the pathogenic microbes in the bone-marrow. As we have just explained, 'agents' of similar quality may sometimes give rise to oligocythaemia and sometimes to polycythaemia, according to quantitative conditions on the side of the 'agent' and 'reactive' conditions

on the side of the affected individual, so that it is not surprising that a disease like tuberculosis or syphilis, frequently causing oligocythaemia, may occasionally give rise to polycythaemia.

A slight polycythaemia, doubtless reactive in nature, has sometimes been observed in early cases of tuberculosis. Mircoli regards it as the effect in particularly constituted individuals of (or what I should call an expression of the reaction of the haemopoietic tissues towards) the circulation of minute amounts of tuberculin in the blood, and Rebaudi and Lionello succeeded in inducing an increase in the number of red cells by injecting minute quantities of tuberculin. Geisböck observed an increase of the red cells to 6,200,000 in a young girl with miliary tuberculosis. The polycythaemia sometimes found in quiescent or obsolete pulmonary tuberculosis, especially in patients under favourable conditions (for instance, under prolonged sanatorium treatment), is probably often compensatory to the fibrotic changes in the lungs. Whether primary splenic tuberculosis really induces the great polycythaemia, which in some cases it has been supposed to, is a question to which we shall again refer in Part II, but we may here mention that Lefas and Bender produced polycythaemia in animals by intrasplenic injection of attenuated cultures of human tubercle bacilli.

Syphilis, though it often leads to oligocythaemia, may occasionally give rise to slight polycythaemia, with which, however, there may be diminution (as in chlorosis) of the haemoglobin-value, so as to give rise to a kind of 'polycythaemic anaemia'. Geisböck has observed considerable temporary polycythaemia (6,100,000 to 8,700,000 red cells) with low blood-pressure during attacks of influenza in three young persons who attracted special attention owing to the red or bluish-red colour of their faces.

*Polycythaemia of suprarenal origin.* It would be interesting to know whether the cyanosis and 'plethoric type of obesity' which have sometimes been observed in connexion with hypernephroma, notably in children (Bullock and Sequeira, L. Guthrie), are ever accompanied by polycythaemia, but unfortunately the blood has seldom, or hardly ever, been examined in such cases from this point of view. Increase in the number of red blood-cells has been experimentally obtained in animals as a result of 'suprarenin' injections, but this may be a merely relative increase, not an absolute erythrocytosis (*vide* O. Hess, 1904).

*Local processes affecting the nutrition of the bone-marrow in regard to the occurrence of polycythaemia.* It is of course well known that disturbances of nutrition in the bone-marrow, such as those caused by toxins circulating in the blood, by the presence and local growth of pathogenic microbes and tumours, and by widespread gelatinous degeneration, may produce obvious morphological changes in the blood. F. Müller ligatured the nutrient artery supplying the marrow of an animal's long bone, and (as a result, he thinks, of deficiency of oxygen in the bone-marrow) after three or four minutes many erythroblasts were found in the blood obtained from the efferent vein. In regard to the possibility

of polycythaemia being sometimes due to direct excitation of the bone-marrow, it may be mentioned that Byrom Bramwell in a case of osteitis deformans (Paget's disease) obtained a blood-count of 6,700,000 red cells to the cubic millimetre with a haemoglobin-value of 105 per cent. Patients with 'angina cruris', 'intermittent clandication,' or actually commencing gangrene from arterial obstruction in one of the lower extremities, manifest occasionally (though rarely, as far as my experience goes, and I have private notes of several cases in which the blood was examined) some degree of polycythaemia. I am indebted to Dr. J. Galloway for showing me a typical example of this combination. His patient was a man over 50 years of age, with typical angina cruris from chronic arterial ischaemia in one leg. Whenever his red blood-cells were counted the number was found to be considerably above the normal, about 7,000,000, for instance, on one occasion. This man had had syphilis, and afterwards became hemiplegic and died, probably from cerebral vascular disease on a syphilitic basis. Geisböck mentions a man, aet. 64, with high blood-pressure and arteriosclerotic gangrene of the right foot, whose blood was found to contain 10–11 million red cells in the cubic millimetre (haemoglobin-value 156 per cent.). Lommel refers to a man, aet. 46, with severe pain and commencing gangrene in the right foot from arterial disease; the blood-count in this man gave 9,700,000 red cells, and the haemoglobin-value was 150 per cent. Erythromelalgia-like symptoms, probably connected with more or less organic vascular changes in the affected limb, have been recorded in several cases of erythraemia (see Part II). In all these clinical observations, however, the exact relation of the vascular disease to the polycythaemia is not quite clear.

### Action and Vital Reaction in regard to Erythrocytosis.

In previous paragraphs I have already referred to the question of the same 'agent' at one time giving rise to oligocythaemia, and at another to polycythaemia. Just as infective 'agents' of like nature in different cases excite very different degrees of leucocytosis, or none at all, so also with regard to the red cells similar agents excite an erythrocytosis in some cases and not in others. Chronic cyanosis of cardio-pulmonary origin may in some cases induce a very marked erythrocytosis, whilst in other cases, in spite of the cyanosis, the number of red cells in the cubic millimetre of blood may be below normal. Doubtless much depends on the 'dose' and duration of action of the 'agent', for, whereas ordinary doses of haemolytic serum cause an oligocythaemia by direct destruction of red corpuscles in the blood, repeated minute doses may actually increase the number of the erythrocytes. In the former case the direct effect of the haemolytic 'agent' predominates, but in the latter case the vital 'reaction' of the bone-marrow is more powerful than the haemolytic 'action' which calls it into play. So also with regard to tuberculin, very minute amounts (in some individuals) may induce an increase instead of a decrease in the number of red blood-corpuscles. In the balance of 'action' and 'vital reaction' much must

depend on the condition of the patient's organism, due to age, sex, habits, the quality of his bone-marrow, and the temporary state of his general health. Reaction on the part of the bone-marrow may be affected by changes in its substance or in the blood-vessels which supply it with nutrient material and oxygen. Besides these obvious factors in regard to the degree of reaction there is the possible occurrence of obscure individual peculiarities or idiosyncrasies to be remembered. Thus, there are some persons whose red blood-corpuscles always show a peculiar susceptibility towards haemolytic agents (A. Chauffard, &c.). We still want information, however, in regard to the possible occurrence of persons congenitally endowed with red blood-cells that manifest a special durability or abnormally great resistance to haemolytic agents.

In regard also to individual peculiarities, one may suppose that, if the activity of the bone-marrow be greatly increased from any cause, erythroblasts or myelocytes more readily escape into the blood-stream in some subjects than in others. This might account for the presence of nucleated red cells in the blood in some cases of erythraemia but not in others. It might also account for the exceptional occurrence of erythroblasts in the blood in the 'polycythaemia of high altitudes' and other forms of erythrocytosis.

Individual peculiarities of reaction may perhaps help to explain the fact that splenomegaly connected with (or actually caused by) obstruction in the portal vein (phlebitis spleno-portalis) may in some individuals be associated with oligocythaemia so as to simulate splenic anaemia, Banti's disease, or Hayem's splenomegaly with chronic jaundice (Oettinger and Fiessinger, Dock and Warthin, &c.), and may in other individuals be associated with polycythaemia so as to give rise to the symptom-complex of splenomegalic polycythaemia (van der Weyde and van Ijzeren, Lommel's first case).

Probably the great differences between different cases of erythraemia in regard to blood-pressure may likewise to some extent be explained as dependent on individual peculiarities of reaction.

### Cases of Polycythaemia of Uncertain Nature.

In Appendix B short notes of various obscure cases are included. Particularly worthy of mention are the cases of polycythaemia in young persons, mostly associated with splenomegaly, of which comparatively few examples have as yet been recorded. These cases are, I believe, by no means so rare as has been supposed.

In regard to the whole subject of polycythaemia, what we now most require is the careful and unbiased study of individual cases, as to their commencement and progress, as to evidence of obstructed circulation not of cardiac or pulmonary origin, as to the presence or absence of chronic toxaemic conditions, and as to the oxygen-capacity of the blood.

## PART II. ERYTHRAEMIA.

*Synonyms:*—'Splenomegalic polycythaemia', 'Myelopathic polycythaemia', 'Polycythaemia with chronic cyanosis', 'Erythrocytosis megalosplenica' (Senator), Vaquez's disease, Osler's disease.

*Definition of Erythraemia.* A disease or morbid condition characterized by well-marked persistent relative and absolute polycythaemia (increase in the number of red blood-corpuscles) due to an excessive erythroblastic activity of the bone-marrow, which appears to be the primary morbid factor in the condition; it is characterized likewise by persistent increase in the viscosity and total volume of the blood, and usually by a cyanotic appearance of the patient and by enlargement of the spleen.

Although the term 'splenomegalic polycythaemia' is included amongst the above-mentioned synonyms of 'erythraemia', it is preferable to employ the term (splenomegalic polycythaemia) in a clinical sense merely, that is to say, as signifying a clinical symptom-complex characterized by a polycythaemia not obviously secondary to blood-stasis and by a splenomegaly for which no local cause (such as obstruction in the splenic and portal veins) is suspected. The results of post-mortem examinations (Reckzeh, van der Weyde and van Ijzeren, Lommel), however, make it certain, as we shall subsequently point out, that in some of these cases the polycythaemia has been more or less secondary to blood-stasis. Such cases, therefore, are not pure examples of erythraemia according to the definition just given, though clinically they are cases of 'splenomegalic polycythaemia'.

*History.* In 1892, H. Vaquez, of Paris, described a peculiar form of cyanosis accompanied by excessive and persistent polycythaemia ('hyperglobulie'), and in a supplementary note (1895) Vaquez drew attention to the existence of splenomegaly and the absence of cardiac lesions in his case. Other early cases of polycythaemia associated with splenomegaly are those recorded by Rendu and Widal (1899), Moutard-Martin and Lefas (1899), R. C. Cabot (1899 and 1900), Cominotti (1900), McKeen (1901), Saundby and Russell (1902), and W. Türk (1902–1904). In a prefatory note to Russell's description of Saundby's case in the *Lancet* the condition was characterized as a 'clinical entity', but it was probably the appearance of two papers by W. Osler (1903 and 1904) that widely drew attention to the subject in England and America. Important papers have been published on the subject in Germany by Rosengart, Weintraud, Lommel, H. Hirschfeld, Senator, and others. L. G. J. Mackey, in 1907, was able to collect over forty cases from the literature. Reports of many more exist, and the writer knows besides of several as yet unpublished cases.[4]

[4] Owing to the kindness of various medical friends, especially Dr. R. Hutchison (3 cases), Dr. Purves Stewart, Dr. T. D. Acland, Dr. H. H. Tooth, Dr. A. F. Voelcker, and Dr. E. Cautley, he has had the opportunity of himself seeing and examining quite a number of published or

Erythraemia cannot be quite so rare as it has been supposed to be. There have been several post-mortem examinations; the first complete one was published by Weber and Watson in March, 1904. In former times cases of erythraemia were probably classified under various headings, such as plethora, general venous congestion with cyanosis, &c. Cuffer and Sollier's two cases (1889) of 'congestive venous diathesis' were perhaps examples of erythraemia.

*Signs and symptoms.* The patient may complain of lassitude, headache, migraine (ophthalmic migraine with 'rainbow-scotoma' or 'teichopsia' in G. Koester's case), vertigo, sensations of fullness in the head or of rush of blood to the head, abdominal pains (especially in the left hypochondriac region), dyspepsia, constipation, distressing thirst, menorrhagia, epistaxis, bleeding gums. Other recorded haemorrhages in erythraemia have been from the stomach, intestines, kidneys, and into the pleural or peritoneal cavities or into the brain. Subjective symptoms may at first sometimes be almost wanting, but usually for some years before the polycythaemia or cyanosis has been observed the patient has suffered from feelings of tension or pains in the left hypochondriac region, pain or sensation of congestion in the head, and loss of strength or lassitude. The vascular engorgement and redness or cyanosis of the skin, most obvious in the face and ears, vary much in different cases and in the same patient at different times. True cyanosis is sometimes quite absent; none was observed in Parkes Weber's second case. Exposure to cold and emotional influences may intensify the cyanosis of erythraemia, just as they sometimes act in other forms of cyanosis. Osler, in his recent 'clinical lecture', points out that a warm room and mental excitement may occasionally cause blueness of the face in these patients to give place to redness. The vascular engorgement is of course not limited to the skin, but may be observed likewise in the mucous membrane of the mouth, fauces and larynx, in the conjunctivae, and by ophthalmoscopic examination in the interior of the eyes. Especially characteristic is the bluish-red appearance of the tongue. Sometimes cutaneous pigmentation, mostly only slight in degree, has been observed. Osler in his recent case drew attention to the fact that a typical so-called 'white line' could be produced by cutaneous irritation, a sign which some French authors have recently supposed to be connected with functional insufficiency of the suprarenal capsules. The spleen can generally be felt moderately or considerably enlarged and hardened, and the liver not rarely reaches below the costal margin. Considerable variation in the size of the spleen from time to time has been observed in one or two cases, and in one of Weintraud's cases the splenomegaly disappeared whilst the patient was under observation. The urine may be either pale and abundant or highly coloured and containing excess of urobilin (Weber and Watson, Türk, &c.), as evidenced, for instance, by spectroscopic examination without concentration of the fluid. It often contains a little

unpublished cases besides his own. Dr. Purves Stewart's case at the Westminster Hospital in 1903 was the first one recognized in London. Dr. Acland's case at St. Thomas's Hospital in 1904 was the first one in which the total blood-volume was estimated.

albumen and sometimes hyaline and granular tube-casts. Occasionally much albuminuria has been recorded, as in Münzer's second case and in Cautley's case, but in the latter considerable organic renal disease was found at the necropsy. Here we may mention that the total excretion of urobilin from the body was found to be slightly above the average in a case of (clinically) splenomegalic polycythaemia reported by Lommel and in Löw and Popper's first case, but it was about normal in two cases reported by Senator. The blood-pressure is frequently, but not invariably, above the normal. In a few cases organic renal disease has doubtless had something to do with the high blood-pressure. In cases of so-called 'hypertonia polycythaemica' (see later on) the brachial systolic blood-pressure, as measured by the Riva-Rocci method, may, according to Mohr, even reach 320 mm. Hg.

*Blood-changes.* The most important signs are of course those yielded by examination of the blood. The red cells are increased in number, generally to between 7 and 12 millions in the cubic millimetre, and on the average they are generally rather increased than decreased in diameter (as Vaquez was the first to point out), but very little attention has, I think, been devoted to ascertaining the average volume of the red cells by J. A. Capps's method. Though the erythrocytes are usually normal in appearance, in Begg and Bullmore's case (a doubtful case, however—see Appendix B, No. 12) they showed poikilocytosis, and marked polychromatophilia; Türk likewise mentions having met with polychromatophilia and slight poikilocytosis. The degree of polycythaemia has in some cases been observed to vary greatly from time to time. The highest erythrocyte-count seems to have been 13,600,000 in Koester's case. In regard to the white cells the only quite constant feature is the excessive proportion of the polymorphonuclears (not rarely up to 80–85 per cent. or higher). The number of white cells is, however, nearly always increased, often up to 20,000 to 30,000 per cubic millimetre. In one case (Parkes Weber) the minimum count was only 4,000, but a still lower figure, namely 1,080, has been noted by Geisböck (Appendix B, 11), unless there was a misprint. Weintraud has recorded as high a count as 54,000. A few normoblasts and one or two myeloblasts have occasionally been noted. In Blumenthal's case in which the white cells numbered 16,300, as many as 36 per cent. of them were myelocytes. The haemoglobin-value may reach even to 170 or 180 per cent. or even higher (the 240 per cent. recorded on one occasion by Koester is scarcely conceivable), but the colour-index is often below 1·0. Nothing abnormal has been found by cryoscopic examination of the blood (Senator, Parkes Weber). The specific gravity of the whole blood is probably always raised, and in Glaessner's case it reached 1,083, but further observations in this respect are required. The dry residue of the blood is doubtless also somewhat increased, whilst the dry residue and specific gravity of the blood-serum seem to be usually diminished (see Part I). The amount of iron in the blood is probably raised in proportion to the excess of haemoglobin. The viscosity of the blood is increased, more or less in proportion to the degree of polycythaemia (see in Part I, the paragraphs on the

Viscosity of the Blood in Polycythaemia). The blood-coagulability is probably sometimes greater and sometimes less than normal. The resistance to haemolysis was found in one case (Vaquez and Laubry) decreased, and in other cases (Parkes Weber, Saundby) about normal. The total blood-volume, as estimated during life by Haldane and Lorrain Smith's 'carbon-monoxide method', is greatly above the normal (as we have already dwelt on in Part I), and this clinical finding is confirmed by the appearance of the viscera as seen at post-mortem examinations (see Appendix A). It is worth mentioning (though the significance is by no means clear) that in two cases of (clinically) splenomegalic polycythaemia Senator found increased activity in the respiratory gas-exchange, and so also did Lommel in the second of his cases.

*Complications.* As occasional complications we may mention jaundice (Türk, Geisböck), hepatic cirrhosis (see Appendix A, 11, 13), renal disease (Appendix A, 10, 23 and 25), ovarian tumour (second case of Parkes Weber), a certain amount of pulmonary emphysema (Appendix A, 7, 12, 24), bronchitis (W. Pfeiffer), bronchiectasis (Kikuchi), slight valvular lesions of the heart (Appendix A, 6, 12), myocardial fibrosis (Appendix A, 15), arteriosclerotic changes, thrombotic infarction of the spleen (Appendix A, many cases), the results of vascular disease in the brain (Appendix A, 4, 15, 22, 23, 25), erythromelagia or erythromelagia-like pain (Türk, Parkes Weber, Cabot, Collins, Lommel, Weintraud), angina cruris of ischaemic origin and arteriosclerotic gangrene of a foot (see Lommel's case and also one of Geisböck's cases of 'hypertonia polycythaemica', abstracts in Appendix B, Nos. 16 and 17), gastric ulcer (Appendix A, 12, 19), pigmentation of the skin, Ménière's attacks, tabes dorsalis (Glaessner), uncontrollable impulses (Cassirer and Bamberger), and insanity (Weber and Watson). Splenic tuberculosis was found in two cases, and in two other cases pulmonary tuberculosis was the cause of death.

*Morbid Anatomy.* There have been post-mortem examinations made in several cases, and an abstract of the results in all these cases is given in Appendix A. Evidence of increased erythroblastic activity in the bone-marrow has been found in almost every case in which the bone-marrow from the shafts of the long bones was examined after death, and in one case G. A. Gibson obtained similar evidence by exploring the condition of the bone-marrow during life. Much of the marrow of the shafts of the long bones which is normally of the yellow fatty kind has been found converted into red (active blood-forming) marrow, so that the total amount of erythrocyte-producing marrow in the body must have been enormously increased, though the red marrow normally present may not have been much altered. A striking feature in Weber and Watson's case (Appendix A, 12) was the large proportion of non-granulated mononuclear cells of the large lymphocyte type (probably to be regarded as 'non-granulated myelocytes' or 'myeloblasts') seen in sections of the altered marrow, doubtless signifying excessive leucoblastic activity. In Blumenthal's case (Appendix A, 21) the marrow contained very much more leucoblastic than erythroblastic tissue; in Westenhoeffer and Hirschfeld's case (Appendix A, 22) likewise the

leucoblastic were in excess of the erythroblastic elements of the marrow. For the most probable explanation of these facts, see later on under 'Pathology and Aetiology'.

The spleen has been almost always found enlarged and engorged with blood, but (in the cases carefully examined) this organ showed little (see Appendix A, 15), if any, erythroblastic transformation; in two cases (Appendix A, 16, 22) Hirschfeld found a certain amount of myeloid change, but this was leucoblastic, not erythroblastic. In this connexion it may be mentioned that in Ascoli's case the spleen was punctured with the consent of the patient during life, and the splenic juice obtained from the puncture was searched for erythroblasts with a negative result. In many cases the spleen contained anaemic infarcts, apparently of thrombotic origin. In one or two cases no enlargement of the spleen was found either during life or after death (Herringham, Blumenthal). The lymphatic glands seem hardly ever to be affected, and when examined microscopically (H. Hirschfeld) they have not presented the least signs of erythroblastic transformation. The enlarged lymphatic glands in Blumenthal's case showed vascular congestion and fibrosis. The extreme vascular engorgement of the liver noted in some cases is quite distinct from that found in 'nutmeg' livers. The liver has been found at most necropsies not to be much altered excepting in regard to vascular engorgement, and in Löw and Popper's first case the relative functional integrity of the organ was confirmed by dietetic tests during life.

In every case examined post mortem the distension of the visceral blood-vessels has been very striking, the mesenteric venules presenting sometimes the appearance of having been forcibly injected for purposes of anatomical demonstration (see Weber and Watson). Amongst occasional findings (see Appendix A) have been a certain amount of pulmonary emphysema, arterio-sclerosis, fibrosis of the cardiac muscle, slight changes in the cardiac valves, hepatic cirrhosis, renal disease, and the results of disease of cerebral blood-vessels. Primary tuberculous nodules in the spleen were reported in two cases (Moutard-Martin and Lefas, Rendu and Widal) in which it was scarcely possible that anaemic infarcts could have been mistaken for tuberculous caseous masses. In Scharold's case of primary splenic tuberculosis, confirmed by post-mortem examination, there was cyanosis, but no blood-count was made, and it cannot be taken for granted that polycythaemia was present. In view of the greatly increased blood-viscosity the absence of very much cardiac hypertrophy in most polycythaemic cases is remarkable.

*Pathology and Aetiology. Explanation of erythraemia as a primary disease of the bone-marrow.* Most of the signs and symptoms of erythraemia may be accounted for by the increased formation of red blood-cells in the bone-marrow, which is evidenced not only by the results of post-mortem examinations, but during life by the high percentage of the polymorphonuclear leucocytes and the occasional presence of erythroblasts and myelocytes in the circulating blood, and in one case (G. A. Gibson) by direct examination of the bone-marrow of

a long bone ('biopsy' method). The results of this excessive erythroblastic activity of the bone-marrow may be compared to what would be the consequences of persistent slow transfusion of blood into the veins of an animal. Experimental sudden transfusion of blood in animals (von Lesser, Worm-Müller) leads to temporary plethora followed quickly by polycythaemia, and it is reasonable to suppose that a slow transfusion of blood, lasting not for a few minutes only but for months and years (were it possible from the experimental point of view), would give rise to a condition of persistent absolute polycythaemia associated with true plethora, such as is met with in cases of erythraemia (see Part I, sections on the Cause of Absolute Polycythaemia and on the Blood-Volume in Absolute Polycythaemia). Dilatation of capillaries and venules would necessarily follow, and probably in most cases, for a time at least, there would be increased arterial blood-pressure. Ultimately degenerative changes in the vascular system would be likely to occur, leading to true passive congestion, cyanosis, bleeding from the gums, thrombosis in various organs, and local circulatory disorders. The excess of the total erythroblastic activity in cases of erythraemia may be supposed to be the primary change giving rise to the clinical symptoms. It may be regarded as analogous to the increased leucoblastic activity in leukaemia, or as a return of the marrow to the condition of foetal activity. In a few cases it appears as if the bone-marrow had never lost its foetal characteristics, and as if the polycythaemia was the result of this 'infantile' (or rather 'foetal') condition of the blood-forming organ (see Blumenthal's case and other cases of polycythaemia commencing in early life—in Appendix A and Appendix B).

That increased leucoblastic activity nearly always accompanies the increased erythroblastic activity in the bone-marrow is evidenced during life by the usually large number of white corpuscles, especially polymorphonuclears, and by the occasional presence of myelocytes, in the circulating blood. At necropsies the examination of the marrow of the shafts of long bones has shown that a decided increase of leucoblastic tissue (see Appendix A, Nos. 12, 22) does accompany the increase of erythroblastic tissue, and probably in most cases the leucoblastic elements occupy more space in the bone-marrow than the erythroblastic elements do. This feature of the bone-marrow seems to have been exaggerated in Blumenthal's case (Appendix A, 15), in which during life 36 per cent. of the white cells of the blood were found to be myelocytes; after death the leucoblastic elements of the bone-marrow were found very greatly to exceed the erythroblastic elements. In fact, Blumenthal's case appears almost to represent a link in a chain, which future observations may discover, connecting erythraemia with myelocytic (myeloid) leukaemia. We fully expect in the future to read of cases showing conditions of the blood and bone-marrow more or less similar to those in Blumenthal's case described as examples of 'Blumenthal's disease'.

It is not quite clear why in erythraemia more of the bone-marrow should consist of leucoblastic than of erythroblastic elements. I think the most probable explanation is that in the marrow of these patients (and probably also in that of healthy individuals) the red cells are much more rapidly produced than are the

white cells by their respective 'parents'. Hence even when the bone-marrow consists chiefly of leucoblastic tissue the red cells far outnumber the white cells in the blood. Moreover, the average life-duration of red cells perhaps exceeds that of white cells.

The enlargement of the spleen which is found in most cases of erythraemia seems to be due partly to engorgement with blood, the organ acting as a kind of elastic blood-reservoir, and partly to hyperplasia of the splenic pulp, possibly connected with the increased haemolysis (see the paragraph in Part I on 'Increased haemolysis in absolute polycythaemia') which must necessarily accompany all conditions of absolute polycythaemia; unless indeed the erythrocytes are specially long-lived, but there is certainly no evidence in favour of the red cells being endowed with special durability (I shall return to this subject later on). The splenic enlargement can certainly not be accounted for by the partial myeloid (leucoblastic, not erythroblastic) transformation that has been found in some cases (Appendix A, 16, 22), and still less so by the presence of erythroblastic foci detected by Ledingham after careful search in one case (Appendix A, 15). Thrombotic infarcts, past malaria, or tuberculosis (see later on) may sometimes partly account for the splenomegaly, and in one or two cases in which great vascular degenerative changes constituted a striking feature there may have been a syphilitic element present. At future necropsies great care should also be taken to examine for changes in the splenic and portal veins. Both splenic infarcts and obstruction in the splenic and portal veins may give rise to more or less splenomegaly. And, though it must be remembered that the presence of disease in the splenic and portal veins in cases of splenomegaly does not necessarily signify that the enlargement of the spleen was entirely secondary to venous obstruction, splenic enlargement in certain cases supposed during life to have been examples of splenic anaemia or Banti's disease (Dock and Warthin, Oettinger and Fiessinger, &c.) has, after death, been found to be connected with obstruction in the splenic vein; so also in two cases characterized clinically by polycythaemia with splenomegaly (van der Weyde and van Ijzeren, and Lommel's first case) the necropsy showed the presence of chronic obstruction in the portal vein.

Erythraemia affects persons of either sex chiefly between the ages of 35 and 50, but has been observed in persons after 60 and several times before 30 years of age; according to the observations of Blumenthal and Ambard and Fiessinger (Appendix A—see also some cases in Appendix B) it may sometimes possibly even be congenital. Nothing is known as to the relation of the condition to climate (atmospheric temperature) and race.

Nervous excitement or mental worry has been suggested as the exciting cause in some cases. According to various theories the abnormal activity of the bone-marrow (giving rise to the polycythaemia) is due to a state of toxaemia having its source in the spleen, lungs, or alimentary canal, or, it is suggested, the polycythaemia may be regarded as the result of a compensatory reaction towards some hypothetical disturbance in the gas-exchanging functions of the blood,

which disturbance might in its turn be of toxaemic (for instance, alimentary, digestive, or metabolic) origin.

The results of post-mortem examinations make it appear that the increased erythroblastic activity of the bone-marrow which gives rise to the polycythaemia cannot be regarded as secondary to blood-stasis (impeded circulation) in most cases of 'splenomegalic polycythaemia', though, as we shall presently have to admit, blood-stasis may occasionally give rise to the same symptom-complex (that is to say, may give rise to polycythaemia with splenomegaly). The increased blood-viscosity (see Part I) necessarily accompanying polycythaemia must, however, favour the *development of a secondary condition of blood-stasis*, whether there be a compensatory increase in blood-pressure (as there usually is in erythraemia) or not. Delayed circulation in its turn favours the occurrence of thrombosis[5] in the various viscera, and the occurrence of thrombosis further hampers the circulation. Again, delayed circulation, and congestion, in the blood-vessels of the lungs and bronchi promote the development of chronic catarrhal changes, which induce cyanosis and throw extra work on the right side of the heart. So that in erythraemia an elaborate *vicious circle* is established; the polycythaemia in various ways tends to impede the circulation, and the blood-stasis thus produced favours cyanosis and increases the circulatory difficulty by giving rise to a further (compensatory secondary) polycythaemia in addition to the primary (myelopathic) polycythaemia.

*Blood-stasis (impeded circulation) in regard to erythraemia and erythrocytosis.* It must be remembered that the blood-stasis and chronic cyanosis resulting from cardiac and pulmonary diseases (especially congenital pulmonary stenosis) sometimes give rise to a secondary polycythaemia (erythrocytosis) quite equal to that observed in many cases of erythraemia (see Part I), and Lommel has endeavoured to show that most cases of erythraemia are really due to blood-stasis (impeded circulation). We believe that the signs of more or less impeded circulation undoubtedly present in many cases of erythraemia are secondary to the polycythaemia in the way we have just explained, and we do not believe that the presence of a certain amount of blood-stasis by any means necessarily signifies that impeded circulation is the chief cause of the polycythaemia. Moreover, although the presence of increased arterial blood-pressure is no sure sign of the absence of any blood-stasis of cardiac or pulmonary origin, the fact that in some cases of polycythaemia with high blood-pressure (the 'hypertonia polycythaemica' or 'polycythaemia hypertonica' of Geisböck and Hess) the number of red corpuscles is almost as great in the arterial as in the venous blood forms a strong argument against blood-stasis playing a large part in the

[5] In some cases of polycythaemia the coagulability of the blood appears to be diminished; the diminution of coagulability in such cases, although it would partially neutralize the tendency of the delayed circulation to favour thrombosis, can scarcely without further evidence be regarded as an automatic vital compensatory change analogous to the compensatory increase in the number of red blood-corpuscles in cases of congenital heart disease and chronic blood-stasis.

causation of the polycythaemia in the cases in question. It must, however, be admitted that blood-stasis, especially when due to chronic obstruction in the portal and splenic veins, may, at least in some individuals,[6] give rise to polycythaemia with splenomegaly, that is to say, may give rise to the clinical symptom-complex 'splenomegalic polycythaemia', which may be mistaken for true erythraemia. The cases of Reckzeh, Lommel, and van der Weyde and van Ijzeren (described in Appendix A) are probably, as Lommel insists, to be explained in this way, and such cases of clinically 'splenomegalic polycythaemia' should not be included as examples of erythraemia according to our use of the latter term, as defined at the commencement of Part II.

We have now considered the prevailing theory of erythraemia, which regards the polycythaemia in these cases as due to a 'primary myelopathy', and we have likewise considered the most important rival theory, which regards the polycythaemia as secondary to blood-stasis, but there are several other theories which have been brought forward, and, though by some writers they have been set up to be knocked down again, we must now shortly consider them.

*Other possible theories of erythraemia*:—(*a*) *Increased durability of the red blood-cells.* There is no practical clinical method for measuring the average life-limit of the red corpuscles. H. Quincke in experiments on animals ascertained the time taken for the blood to return to its normal state after the artificial production of plethora. By his observations he estimated the normal average duration of life of the red cells at two to five weeks, but G. Froin by other methods of observation has estimated it at a much higher figure. Fick (quoted by G. Schroeder) suggested that the 'polycythaemia of high altitudes' was due to an increased durability of the red cells resulting from residence in mountain resorts. But, as pointed out in Part I, it is almost certain that this polycythaemia of high altitudes is due to a genuine increase of the erythroblastic activity of the bone-marrow. Certainly in regard to the polycythaemia of erythraemia there is no evidence forthcoming that it is due to increased life-duration of the red cells, but on the contrary there is some evidence pointing to the total haemolysis in the body being increased, as one would expect it to be, in all cases of absolute polycythaemia. We have already dealt with this subject in Part I, under the heading 'Increased haemolysis in absolute polycythaemia', and need not add anything further to what we have already stated there.

(*b*) *Diminished oxygen-capacity of the haemoglobin,* that is to say, diminution in the amount of oxygen that the haemoglobin will take up as compared to the amount taken up by the haemoglobin in normal blood. Bence and von Koranyi suggested that absolute polycythaemia might in some cases be the result of a compensatory reaction towards some impairment in the quality of the haemoglobin which diminishes its oxygen-capacity. Mohr and Lommel have likewise paid attention to this question. Mohr actually found decided

[6] As already explained, the erythropoietic reaction towards blood-stasis appears to vary much in different individuals. See Part I, Section on 'Action and Vital Reaction in regard to Erythrocytosis'.

diminution of the oxygen-capacity of the haemoglobin in a case of congenital pulmonary stenosis with secondary polycythaemia (erythrocytosis). It must be remarked, however, that in cases of methaemoglobinaemia and sulph-haemoglobinaemia, in which the oxygen-capacity has been lowered owing to some of the haemoglobin in the erythrocytes becoming changed into methaemoglobin or sulph-haemoglobin, no secondary polycythaemia has been observed, and in a few cases of erythraemia (Saundby and Russell, Tooth, Herringham) the presence in the blood of methaemoglobin or sulph-haemoglobin has been excluded by spectroscopic examination. Moreover, in cases of polycythaemia with splenomegaly, whether actually cases of erythraemia or not, the oxygen-capacity of the haemoglobin has never been found notably reduced. In two cases of Lommel and one of Mohr it was found to be at the lowest level within normal limits. Nor was Bence's suggestion supported by Senator's results or by two cases (referred to by Parkes Weber, 1906) in which A. E. Boycott examined the oxygen-capacity of the blood.

(*c*) *Possible toxic and infectious causes.* In regard to the possibility of polycythaemia resulting from various toxic and infectious causes we must refer to the paragraphs in Part 1, on 'Erythrocytosis of Toxic Origin' and 'Erythrocytosis in Chronic Infectious Diseases'. In cases of erythraemia, or at all events of (clinically) 'splenomegalic polycythaemia', chronic toxic or infectious conditions have not rarely been present, for instance, disorders of the digestive canal accompanied by a coated tongue, tuberculous nodules in the spleen, bronchiectasis (Kikuchi) and otorrhoea (Ascoli). Kikuchi in his case thought that the bronchiectatic trouble might be acting on the bone-marrow as it acts on the bones in the cases in which it gives rise to Marie's so-called 'pulmonary hypertrophic osteoarthropathy'. In one or two cases of (clinically) splenomegalic polycythaemia there has been clubbing of the fingers, a condition generally supposed to be often partly toxaemic in origin, though often partly due to local blood-stasis.

Syphilis and malaria, like tuberculosis, have been suspected in some cases, but there is little to be said in favour of any one toxic or infectious condition playing an important part in the aetiology of erythraemia. Possibly they may in some cases act as exciting causes, that is to say, as giving a starting stimulus to the bone-marrow, just like in other cases the erythroblastic reaction following a haemorrhage or the disturbance caused by the fracture of a rib or long bone might be supposed to do. There is scarcely more to be said in favour of toxaemia connected with chronic constipation and gastro-intestinal disorders as the cause of so rare a condition.

Splenic tuberculosis, though present in two cases (Rendu and Widal, Moutard-Martin and Lefas), was absent at all the more recent necropsies, and many patients have been submitted to the tuberculin test (Preiss, Weber, Horder, Löw and Popper's first case) with negative results. Primary tuberculosis of the spleen was found by Scharold (1883) at the necropsy on a man aged 25 years, in whom a peculiar alternating redness and cyanosis of the face

had been observed during life. No blood-count was made, and the presence of polycythaemia can scarcely be taken for granted in Scharold's case, especially as in a case of acute miliary tuberculosis of the spleen recorded by D. D. Stewart (1901) examination of the blood showed complete absence of any polycythaemia, in spite of a tendency to cyanosis having been noted. Moreover, tuberculosis of the spleen is by no means always accompanied by polycythaemia (Bayer). Altogether, the theory that the typical symptom-complex of chronic splenomegalic polycythaemia in human beings can result from splenic tuberculosis needs confirmation, in spite of the experiments by Lefas and Bender on animals, who produced polycythaemia by the intra-splenic injection of attenuated cultures of human tubercle bacilli. However, it must be admitted that local tuberculosis may cause splenic enlargement, and that small amounts of tuberculin (see Part 1), whether produced by tubercle bacilli in the patient's own body or injected therapeutically, may, in specially constituted individuals, give rise to a secondary polycythaemia. Therefore splenic tuberculosis must be admitted as a possible occasional cause of both splenomegaly and a certain degree of polycythaemia, if not of the typical symptom-complex, chronic splenomegalic polycythaemia.

In one or two cases of erythraemia pathogenic organisms have been searched for (Herringham, Hutchison and Miller), in the blood during life or in the tissues after death, with negative results.

*Subdivision of cases of erythraemia.* We have already excluded certain cases of (clinically) 'splenomegalic polycythaemia' as being probably due to blood-stasis and therefore not coming under our definition of erythraemia (given at the commencement of Part II). The remaining cases of splenomegalic polycythaemia, and erythraemia without splenomegaly, may be subdivided into different groups according to whether the blood-pressure is very much raised or not, or according to whether the spleen is enlarged, as it usually is, or apparently not enlarged (Herringham, W. Pfeiffer, &c.). We may provisionally class in a group by themselves the cases of absolute polycythaemia with high blood-pressure and without obvious splenic enlargement, that is to say, the cases of 'hypertonia polycythaemica' or 'polycythaemia hypertonica' of Geisböck and Hess. Needless to say, in regard to the high blood-pressure in such cases the question of the presence or absence of organic renal disease must always be taken into account. Equally worthy of a special place is a group of cases commencing in early life. These two groups we shall now shortly consider.

*Polycythaemia hypertonica without splenomegaly.* F. Geisböck, in examining the blood of patients with increased blood-pressure, found that the number of red corpuscles was in some cases increased up to 8–11 millions in the cubic millimetre of blood, and his observations have been confirmed by O. Hess and others. This polycythaemia was nearly as well marked in the arterial as in the venous blood. The patients were beyond middle age, mostly between their fiftieth and sixtieth years, and were red in the face, suggesting the 'habitus apoplecticus' of older medical writers. There was apparently no evidence of splenomegaly. Most of the cases showed a little cardiac enlarge-

ment; in several the urine contained a trace of albumen; in a few there was distinct arteriosclerosis or renal disease; several of the patients had suffered from apoplectiform attacks; and one of them (a man aet. 64) had arteriosclerotic gangrene of the right foot. One patient (a man aet. 55) was much improved by long-continued treatment with iodothyrin. Of another case, decidedly relieved by venesections, and very carefully investigated by Geisböck, we must quote some details. The patient was a man, aet. 54, whose father had died from cerebral haemorrhage. He denied ever having had any venereal disease, but had been accustomed to drink a good deal of beer and smoke much tobacco. He suffered from headaches and occasional giddiness. His skin was red, but not cyanotic. The heart was very slightly enlarged (as shown by percussion and by orthodiascopy with Röntgen rays). The systolic brachial blood-pressure (Riva-Rocci apparatus) was 200–210 mm. Hg. The liver and spleen were not enlarged. The urine, rather abundant and of somewhat low specific gravity, showed an occasional trace of albumen, but no tube-casts. The blood-count gave between ten and eleven million red cells to the cubic millimetre. The haemoglobin-value was 140 to 185 per cent. The specific gravity of the blood-serum and the amount of its dry residue were not increased, showing that the polycythaemia was not due to blood-concentration. Moreover, on one occasion Geisböck was able to compare specimens of this patient's blood taken at the same time from the radial artery, the tip of the finger and the median vein respectively, and he found very little difference between the three specimens. The erythrocyte-count of the arterial blood gave 10,530,030; of the capillary blood 10,695,000; of the venous blood 10,775,000.

*Congenital erythraemia and erythraemia commencing in early life.* We have already alluded to this group in the Section on 'Pathology and Aetiology'. Short abstracts of Blumenthal's, and Ambard and Fiessinger's cases, of which post-mortem records have been published (very incomplete in the latter case) are given in Appendix A; and in Appendix B we have included short notes on cases of Minkowski, Nichamin, and Hann. In such cases it is possible that the bone-marrow of the shafts of the long bones may early in the patient's life have reverted to its foetal erythroblastic activity, or indeed this foetal character may never have been entirely lost (as it normally should be early in extra-uterine life). Blumenthal's case, which was fully examined after death, is further remarkable for the extraordinary leucoblastic activity, which accompanied and relatively greatly exceeded the erythroblastic activity (in this respect, however, compare post-mortem results, Appendix A, cases Nos. 12 and 22). This leucoblastic activity, the existence of which was confirmed after death by the large amount of leucoblastic marrow present in the shaft of a long bone, was manifested during life by the count of about 5,868 myelocytes in the cubic millimetre of circulating blood. The case, therefore, to some extent, as already stated, appears to connect erythraemia with myelocytic (myeloid) leukaemia.

In connexion with these cases of erythraemia in early life the question

may be asked, Do they perhaps represent an extreme degree of what may be roughly termed the congenital plethoric tendency normal to some individuals, in other words, the 'plethoric type' of person whose food is popularly said 'all to turn into blood'?

*Diagnosis of erythraemia.* The plethoric or cyanotic appearance of the patient, the presence of splenomegaly of uncertain origin, erythromelalgia-like symptoms (as in my second case), or other circumstances, may lead to examination of the blood. The diagnosis of erythraemia then depends, as we have already pointed out, on the recognition of a condition of persistent absolute polycythaemia and the absence of obvious cause for any considerable 'erythrocytosis' (secondary polycythaemia). Splenomegaly, due to causes other than erythraemia, such as passed malaria, syphilis, or chronic obstruction in the splenic or portal veins, if it occurs in association with some form of secondary polycythaemia (erythrocytosis), may doubtless give rise to great difficulties in diagnosis. As a matter of fact, however, the spleen can seldom be felt below the ribs in patients with congenital or acquired cardiac disease. In polycythaemic cases I consider that enlargement of the liver, if present without obvious enlargement of the spleen, is a point somewhat in favour of the increase in the red cells being secondary to blood-stasis.

*Prognosis and Course.* Some cases seem to be almost non-progressive, or seem to improve, at all events for a time, with or without special treatment. Some have died (see Appendix A) in a sudden exacerbation of cyanosis (Herringham, Weber and Watson). Others have died from complications due to vascular disease in the brain (Cabot, Westenhoeffer, Cautley, Hutchison and Miller, Löw and Popper), or from tuberculosis (see Appendix A, No. 1) and intercurrent causes.

*Treatment.* Subjective improvement seems to have followed spontaneous haemorrhages (Weintraud), and treatment by an occasional copious blood-letting has been carried out with at least temporary relief of symptoms in an as yet unpublished (splenomegalic) case by Dr. T. D. Acland. In two or three other splenomegalic cases also, including Cautley's case and an unpublished one kindly shown me by Dr. R. Hutchison, venesection has been tried with apparently temporary benefit. Moreover, in one of Geisböck's cases of 'polycythaemia hypertonica' without splenomegaly (already referred to) great relief was obtained by venesections. On the other hand, in a case of polycythaemia with low blood-pressure (see Appendix B, No. 11) Geisböck observed no improvement worth mentioning from a bleeding of 260 c.cm. (Treatment in that case at Carlsbad had a better result.)

In a case of moderate polycythaemia (with history of malaria), reported by Schneider, excision of the enlarged spleen was resorted to, and the number of red cells decreased, but shortly after the operation the patient developed progressive pulmonary tuberculosis. In Comminotti's case death from sepsis occurred six weeks after the operation. In another case the operation of splenectomy was fatal from internal haemorrhage (Axel Blad). In van der Weyde

and van Ijzeren's case of (clinically) splenomegalic polycythaemia splenectomy was followed by the patient's death 25 days after the operation. Derüschinsky's case, in which no alteration in the blood followed successful removal of an enlarged spleen, though often quoted in this connexion, was never polycythaemic. We may here note that in one case (Lauenstein) of removal of the normal spleen for traumatic rupture of its capsule the number of red corpuscles in the blood at first fell, but then rose, so that 5 weeks after the operation 5,800,000 were counted in the cubic millimetre. Lauenstein's case is, however, probably only an example of temporary polycythaemia following splenectomy, of which other examples are known, but in Schupfer's recent case of removal of the spleen for primary splenomegaly (see Appendix B, No. 18) the patient 3 years after the operation showed cyanosis of the extremities and polycythaemia with 6,270,000 red cells in the cubic millimetre of blood. Before the operation his red cells were counted at 2,880,000 to 4,920,000.

The application of Röntgen rays did no good in my second case, nor did it improve the general condition in a case (with low blood-pressure) mentioned by Geisböck (see Appendix B, No. 11), but I have heard of apparent improvement from their use in a case under Dr. H. H. Tooth's care at St. Bartholomew's Hospital, and of a decided benefit in a case of which Dr. T. J. Horder has kindly given me details (see Appendix B, Case No. 12; there is, however, some doubt as to the nature of the case). Arsenic, quinine, thyroid substance, vaso-dilators (erythrol tetranitrate or sodium nitrite), and a variety of drugs have been tried, but generally without any satisfactory effect. One of Geisböck's patients with 'polycythaemia hypertonica' (see Appendix B, No. 14) was greatly improved by a long course of iodothyrin. Begg and Bullmore recorded improvement in their case (a doubtful case, see Appendix B, Case No. 12) from quinine and inunction of iodide of mercury ointment. Bence thought that the polycythaemia could be reduced by oxygen inhalations, but Stern was not able to record any such result. In Münzer's second case inhalation of oxygen failed to reduce the blood-viscosity.

On general principles one would, as far as possible, avoid mental fatigue, excitement, and impure air, prevent constipation, caution against excess of tea, coffee, tobacco, and stimulating meats and spices, prohibit alcohol owing to its action on the blood-vessels, chalybeate drugs owing to their effect on the erythroblastic tissues, and coal-tar products such as antipyrin, phenacetin and acetanilid, which by their action on the haemoglobin in the blood occasionally produce cyanosis. The plentiful use of German 'sour milk' or some similar preparation, on account of the effect on the flora of the large intestine, might be worth a trial in some cases, and a lacto-vegetarian diet (Stern), or one rendered as poor in iron as possible (P. Ehrlich), has likewise been suggested.

## APPENDIX A

### Necropsy Findings in cases of Erythraemia and cases clinically characterized by Polycythaemia with Splenomegaly.

(1) H. Vaquez (1892 and 1895).—A man, aet. 40, with chronic cyanosis and polycythaemia. Red cells over 8,000,000. Haemoglobin (by Malassez's method) 165 per cent. Spleen and liver both greatly enlarged. He died of acute tuberculosis, and the necropsy confirmed the presence of enlargement of the spleen and liver and the absence of cardiac disease.

(2) Rendu and Widal (1899).—Man, aet. 30. Illness commenced with feeling of discomfort in the left hypochondrium several years before his death. The spleen reached downwards to the ilium. Liver somewhat enlarged. Much cyanosis. Red blood-cells, 6,200,000; later on only 5,250,000. Increase of dyspnoea and death. At the *necropsy* the spleen was firmly attached by old adhesions to surrounding structures; it was fibrotic, and contained caseous masses. There was tuberculosis of other viscera. The bone-marrow was thought to show evidence of over-activity.

(3) Moutard-Martin and Lefas (1899).—Woman, aet. 49. Red blood-cells 8,200,000. White blood-cells 31,400. No cyanosis. Splenomegaly. Slight enlargement of the liver. Death with vomiting and diarrhoea. At the *necropsy* the enlarged spleen showed scattered caseous nodules, apparently tuberculous.

(4) R. C. Cabot (1899).—Woman, aet, 46, masseuse. About 7 years before her death she had an attack of temporary loss of consciousness. 4 years later she suffered from periods of mental and muscular debility with cyanosis and congestion of the face. Spleen apparently not enlarged. Red cells over 10,000,000. Haemoglobin 150 per cent. She died of middle meningeal haemorrhage, and the post-mortem examination (as far as it went) showed nothing beyond this, except great congestion of the viscera.

(5) V. Cominotti (1900).—Woman, aet. 33. Her father died of spinal caries. She suffered from pains in the situation of the spleen, epistaxis, and headaches. Cyanosis. Splenomegaly. Some enlargement of the liver. Splenectomy was performed and the patient died of sepsis about 6 weeks after the operation. The red blood-cells were about 7 million to the cubic millimetre before the operation; after the operation the number sank to 6,000,000 and then to 5,300,000. It is remarkable that even with the high counts before the operation the haemoglobin-value was estimated at only 80 per cent. The spleen was large and showed fibrous increase. At the *necropsy* in addition to the septic changes in the abdomen caries of the dorsal spinal column was discovered.

(6) Saundby and Russell (1902).—Man, aet. 48. Red cells 7 to 9 millions. Chronic cyanosis. Slight jaundice and increasing drowsiness before death. At the *necropsy* the heart showed slight old mitral valve disease, and there was some hypertrophy. The bronchial tubes contained a good deal of muco-purulent secretion. The spleen was enlarged, but is stated to have been of normal consistence on section; apparently no microscopic examination was made. The bone-marrow of the femur was described as normal to naked-eye inspection. Russell saw the patient with an enlarged spleen several years before any cyanosis was observed. The records of several cases, however, and notably Parkes Weber's second case, show that cyanosis by no means always accompanies erythraemia; the absence of cyanosis cannot therefore be accepted as necessarily signifying the absence of polycythaemia.

(7) W. Osler (1903).—Man, aet. 46. For 20 years slight cough off and on and headaches. Failing strength last 6 years. Cyanosis 4 years. Some

cutaneous pigmentation. Spleen not felt. Red blood-cells 8,250,000. Death occurred after a few hours' drowsiness deepening into coma. The cyanosis in this case rivalled that of congenital heart disease ('morbus caeruleus') so that the patient was known as the 'blue baby'. At the *necropsy* the heart was about normal, the lungs were moderately emphysematous, and the spleen was a little enlarged; but full notes were not available.

(8) A. J. van der Weyde and W. van Ijzeren (1903).—Woman, aet. 44. Chronic cyanosis. Some enlargement of the heart. Great enlargement of the spleen. Blood examined for methaemoglobin with negative results. Red blood-cells 7,600,000; white cells 12,800 (of which 84·7 per cent. were polymorphonuclear neutrophiles). Splenectomy was performed and the patient died 25 days after the operation. The *necropsy* showed great dilatation of the veins in the portal circulation, thrombosis of the portal vein, and thickening of the hepato-duodenal ligament from old inflammation. The spleen was found to have undergone a kind of fibrosis. The kidneys were normal. In this case it is remarkable that with the increase in erythrocytes the haemoglobin-value was estimated at only 90–95 per cent.

(9) R. Breuer (1903).—A woman, aet. 52. Chronic cyanosis with enlargement of spleen and liver. Slight albuminuria and cardiac enlargement. Death was due to internal haemorrhage after removal of a large uterine fibromyoma. At the *necropsy* the bone-marrow of the long bones was found to be in a state of haemopoietic over-activity. The spleen apparently gave no evidence of there being any erythrocyte-formation in progress (no groups of erythroblasts were seen) but it contained great quantities of eosinophile cells.

(10) W. Türk (1904).—Woman, aet. 43. Erysipelas 3 years ago. Phlebitis in left leg 5 months ago. Right facial paralysis. Attacks of temporary aphasia. Neuro-retinitis on both sides. Much cyanosis. Red blood-cells 7½ millions. Urine contained albumin with epithelial and other tube-casts. She died comatose. The *necropsy* showed nephritis and hypertrophy of the left cardiac ventricle. Extreme engorgement of the viscera with blood. The spleen was enlarged and contained multiple anaemic infarcts.

(11) W. Türk (1904).—Woman, aet. 35. Headache and pain in right hypochondrium 1½ years. Enlargement of the liver and spleen. Jaundice. Excess of urobilin and a little bilirubin in the urine. Wasting. No cyanosis or special redness of the face. Red blood-cells about 8 millions; white cells about 10,000; a few erythroblasts and a few myelocytes present. Death with increase of jaundice and haemorrhage from the nose and alimentary canal. The red blood-cells diminished in number to 5,160,000 before death. The *necropsy* showed cirrhosis of the liver with regenerative changes (multiple adenomata). The spleen was large, adherent to the liver, and of firm consistence. The bone-marrow in the long bones was dark red in colour and of fairly firm consistence.

(12) F. P. Weber and J. H. Watson (1904).—The patient was a man aged 58 years, who had always been very ruddy in the face, though strictly temperate with regard to alcohol. He had apparently usually enjoyed fair general health, though always inclined to 'indigestion' and constipation. A tendency to blueness of the nose and extremities had been noticed during the last 6 or 7 years. Latterly he had been subject to feelings of giddiness and prostration which prevented him from following his employment. At the end of 1903, some time after an injury (fracture of ribs), he began to suffer from delusions and had to be sent to a lunatic asylum, where, in spite of apparent mental improvement, he seemed to get weaker. Red blood-cells 9 to 11 millions. White cells 7,500 to 12,000, of which about 82·4 per cent. were neutrophile polymorphonuclears. Haemoglobin-value about 170 per cent. Brachial blood-pressure increased. Urine showed excess of urobilin. The patient died

suddenly of syncope during a period of increased cyanosis. The *post-mortem examination* showed the presence of a certain amount of pulmonary emphysema, slight old disease of the aortic valves of the heart, and an ulcer of the pyloric region of the stomach, but these changes were quite insufficient to account for the enlarged spleen, and for the polycythaemia, and the other symptoms observed during the patient's life. Moreover, the liver had not the typical 'nutmeg' appearance of chronic passive congestion, as it would have had if the enlargement of the spleen had been due to pulmonary emphysema and cardiac disease. On the other hand, the examination of the patient's bones showed that almost all the ordinary yellow (normal) marrow of the shafts of the long bones was in this patient replaced by red marrow from which fat cells were nearly absent, in other words, the amount of erythrocyte-forming tissue in this man's body was immensely greater than in the bodies of ordinary persons. It became, therefore, obvious that even if the formation of red blood-corpuscles had not been particularly active in any one part of the bone-marrow, the total production of red cells in the patient's body must have been very greatly above the average, owing to the great excess of the tissues engaged in manufacturing them. The enlargement of the spleen seemed to be due merely to increase of the splenic pulp and engorgement with blood. The organ was certainly not the site of any active erythropoietic or myeloid change. A striking feature in microscopic sections of the bone-marrow was the large proportion of non-granulated mononuclear cells of the 'large lymphocyte type', probably to be regarded as 'non-granulated myelocytes' or 'myeloblasts'. In the light of later researches there can be no doubt that the bone-marrow in this case was the site of excessive leucoblastic as well as erythroblastic activity.

(13) Axel Blad (1905).—Woman, aet. 34. Pains in epigastrium and left hypochondriac region. Face congested. Splenomegaly. Liver felt below ribs. Red blood-cells 11,000,000. The spleen was excised and death occurred a few hours after the operation. The *necropsy* showed that death was due to profuse internal haemorrhage. The spleen contained some small infarcts, and microscopical examination seemed to show that its enlargement was due to simple hyperplasia. The liver was slightly enlarged, and microscopic examination showed early cirrhotic changes. The condition of the bone-marrow is not stated.

(14) P. Reckzeh (1905).—Reckzeh's third case of polycythaemia with chronic cyanosis and splenomegaly was that of a man aged 24 years, in whom there was progressive compression of the vena cava superior by a malignant tumour of the thymus. The cyanosis and polycythaemia were limited to the territory of the superior vena cava till towards the end of life. On May 2, 1904, the red cells in blood from the upper part of the body were 6,200,000, and from the lower part of the body, 5,100,000. On May 24 the respective counts were 7,100,000 and 6,800,000, and on May 30, 6,500,000 and 6,000,000. With increase of weakness and mental stupor the patient died on June 5. The *necropsy* showed that the tumour of the thymus had extensively involved the right lung, and there were metastatic growths in the brain, kidneys, pancreas and elsewhere in the body. In regard to the cause of the final general polycythaemia in this case it should be noted that the right lung was extensively involved by the tumour and that the right bronchus was compressed by an infiltrated and enlarged lymphatic gland. The substance of the enlarged spleen was soft in consistence and deep red in colour. The bone-marrow was apparently not examined.

(15) R. Hutchison and C. H. Miller (1906).—Man, æt. 45. Red blood-cells $7\frac{1}{2}$ to 11 millions. White cells 17,160 to 22,000. Cyanosis. Spleen extended to umbilicus. Death with coma and hyperpyrexia. *Necropsy*:—Thrombotic softening in occipital lobes of brain. Myocardial fibrosis. The viscera extremely congested. The enlarged spleen was connected by dense adhesions to surround-

ing structures, and contained necrotic patches apparently due to thrombotic infarction. The splenic pulp was carefully searched for the detection of erythroblastic foci, and a very few minute clumps of proliferating nucleated red cells were observed, but in view of their small size and number J. C. G. Ledingham (in his special report) concluded that the spleen had not been exercising any important function as an erythrocyte-forming organ. The bone-marrow from the shaft of the left femur was red in colour, and Ledingham reported :—' One could not conclude from a single section that red blood-cell formation was actively proceeding, but when one reflects that large tracts of marrow were in a similar condition one must infer that the polycythaemia is to be explained by a general increase of the erythroblastic functions of the marrow.'

(16) H. Hirschfeld (1906).—Man, æt. 51. Left-sided haemothorax. The blood was not examined during life. At the *necropsy*, in spite of the large pleural haemorrhage, the viscera were found to be extremely engorged with blood. The bone-marrow in the long bones was mostly red, and microscopic examination showed proliferation of the cellular elements, notably of the normoblasts and giant-cells, but not of mast-cells. The spleen was enlarged and contained a big cyst with sero-sanguineous contents. The splenic substance showed a partial myeloid transformation, which was, however, almost entirely leucoblastic (granulated cells) not erythroblastic; very many cell-containing phagocytes were present.

(17) K. Glaessner (1906).—Man, æt. 44. Syphilis 20 years ago. Pain in the left side of the abdomen 14 years. Dyspnoea seven or eight years. Tabes dorsalis. General cyanosis. Red blood-cells 10 to 11½ millions. Death with right-sided hemiplegia and great dyspnoea. The *necropsy* (apart from the changes in the nervous system) showed the characteristic extreme engorgement of the viscera with blood. The long bones contained areas of bluish-red marrow (erythroblastic marrow) replacing fatty marrow. The spleen was large and showed scattered yellow nodules.

(18) F. Lommel (1906).—Man, æt. 42. Great injection of superficial veins. Splenomegaly. Liver somewhat enlarged. Red blood-cells 8,230,000 to 8,600,000. Haemoglobin (with the lowest erythrocyte figure) 140 per cent. by Sahli's method. The illness had commenced three years ago with headache and feeling of congestion in the head and of pressure in the abdomen. There were frequently recurring pains in the abdomen. Venesection (150–200 c.cm.) was repeatedly performed with temporary subjective relief. Unusually severe abdominal pains were followed by collapse, vomiting, melaena and death. The *necropsy* showed extreme congestion of the portal tributaries (accompanied by angioma-like formations), apparently due to chronic obstruction in the portal circulation. Great thickening of the hepatoduodenal ligament. Recent thrombosis of the portal, splenic and superior mesenteric veins. The substance of the spleen was harder than normal. The bone-marrow (humerus, sternum and ribs) was deep red in colour, and no fatty marrow was seen.

(19) N. Schneider (1907).—Man, æt. 51. He had formerly suffered from malaria. In April, 1901, he was found to have polycythaemia (6,000,000 red cells, 22,000 white cells) and splenomegaly. The spleen was removed in May, 1901, and was found to contain some anaemic infarcts and the capsule was thickened from old perisplenitis, but no careful microscopic examination was made. In June, 1901, the blood-count showed 4,500,000 red cells and 16,000 white cells. Signs of pneumonia in December, 1901, were followed by progressive pulmonary tuberculosis. In April, 1902, the number of red cells was again above the normal, but then decreased until the patient's death, which occurred in October, 1902. On the day of death the red cells numbered only 1,385,000; the white cells numbered 55,400, of which 87·8 per cent. were polymorphonuclears and 1·4 per cent. were myelocytes; there were about twice as many nucleated red

cells (normoblasts) present as white corpuscles. The *necropsy* showed advanced pulmonary tuberculosis, dilatation and hypertrophy of both sides of the heart, with myocardial fibrotic changes in the walls of the left ventricle, aortic atheroma, chronic indurative nephritis, and an ulcer of the pyloric region of the stomach. The bone-marrow of the shafts of the long bones was red. It is not quite clear that Schneider's case was one of erythraemia according to our definition of the term (Part II).

(20) L. Ambard and N. Fiessinger (1907).—A woman, rather beyond middle age, corpulent, plethoric-looking, and very cyanozed. She had been cyanozed and dyspnoeic as a child as if she had congenital heart disease. Her general condition had much improved on the commencement of menstruation, but at the menopause she again became cyanozed and dyspnoeic. Red cells 7,800,000; later on (a month before death) 5,615,000. Dropsy. Death. The *necropsy* showed chronic interstitial nephritis and hypertrophy of the left ventricle of the heart. No valvular disease except slight thickening of the aortic cusps. The spleen was not enlarged, and to naked-eye examination the splenic substance appeared normal. The liver was engorged with blood, but macroscopically and microscopically did not resemble a 'nutmeg liver'. The bone-marrow, owing to a mistake, was not examined.

(21) R. Blumenthal (1907).—Woman, æt. 31. From two years of age she was subject to attacks of paroxysmal dyspnoea, accompanied by severe headache and followed by copious expectoration. From the age of 21 years: cyanosis, debility, haemorrhages. Red blood-cells 11,450,000; white cells 16,300, of which 36 per cent. were myelocytes; no nucleated red cells; haemoglobin 110 per cent. The appearance of the patient's face somewhat resembled that of patients with Graves's disease, but in addition it was extremely congested. By ophthalmoscopic examination the retinal veins were seen to be tortuous and engorged with blood. The *necropsy* showed fibrous adhesions of the right pleura and bronchopneumonia of the lower lobe of the left lung. The bronchial lymphatic glands were very large and of reddish-brown colour. There was a remarkable varicose condition of the veins of the dura mater, and a small haemorrhage was found in the hypophysis cerebri. The heart was somewhat hypertrophied. The capsule of the liver was thickened in places. There was no disease of the kidneys. The bone-marrow from the shaft of the humerus was red and succulent, like foetal marrow; by microscopic examination the leucoblastic tissue was found to be markedly in excess of the erythroblastic. Microscopic examination of the enlarged lymphatic glands showed great richness in blood-vessels, congestion, and fibrosis. Microscopic examination of the liver showed passive congestion and some increase in the interacinous connective tissue. Microscopic examination of the spleen gave no evidence of erythroblastic or myeloid transformation. Blumenthal regards the case as probably of congenital origin. The case is remarkable for the excessive leucoblastic activity, evidenced by the large number of myelocytes present in the circulating blood, and by the results of microscopic examination of the bone-marrow after death. It should, however, be remembered that, though the leucoblastic was decidedly in excess of the erythroblastic tissue, yet, owing to the foetal-like condition of the marrow in the shafts of the long bones (normally occupied by fatty marrow), the total amount of erythroblastic tissue in the body must have been very greatly in excess of the normal.

(22) Westenhoeffer and H. Hirschfeld (1907).—Man, æt. 28, supposed to be suffering from meningitis. No blood-count was made during life. The *necropsy* showed cerebral haemorrhage, but not meningitis. The viscera were all extremely engorged with blood, and so was the bone-marrow, all the cellular elements of which were increased, the white cells more so than the erythroblasts. The normal fat had entirely disappeared. The white cells in the bone marrow could

be divided into two groups: (1) granulated and (2) non-granulated, the latter resembling the so-called 'Rieder's lymphocytes'. The normoblasts were mostly arranged around clusters of these lymphocytes, as if they were genetically allied to them. Although the nucleated red cells were not relatively in excess, it was clear that their total number in the bone-marrow of the whole body must have been enormously increased. The spleen was large, and this enlargement appeared to be due chiefly to engorgement with blood. The Malpighian follicles seemed rather smaller than the average. The slight myeloid transformation detected in the spleen was of the leucoblastic, not of the erythroblastic, kind; erythroblasts were present in only very small numbers, and so they may have been carried there in the blood-stream. Very few cell-containing phagocytes were seen. The lymphatic glands were examined macroscopically and microscopically, and showed nothing abnormal beyond the general hyperaemia.

(23) E. Cautley (1908).—Man, aet. 47. Tender swelling in the splenic region. The colour of the face varied from deep red to a cyanotic tint. Red blood-cells $7\frac{1}{2}$ to 10 millions. Albuminuria. Death occurred from cerebral haemorrhage. The *necropsy* showed granular kidneys and cardiac hypertrophy. The enlarged spleen was firmly adherent to the surrounding structures, and contained two infarcts; the soft splenic tissue was divided into lobules by fibrous bands. Cautley adds that most of the post-mortem appearances could be explained as the result of local thrombosis of the extremely viscid blood. Cautley does not think that the microscopic examination of the bone-marrow or of the various organs afforded any indication of the aetiology of the condition. I understand, however, that the bone-marrow from the shaft of a long bone was red in colour.

(24) W. P. Herringham (1908).—Woman, aet. 38. At one time she was said to be anaemic, but afterwards she was high-coloured and subject to attacks of shortness of breath with lividity. Red cells 7,630,000. Haemoglobin 120 per cent. She died in one of her attacks of dyspnoea and cyanosis. At the *necropsy* the lungs were emphysematous, but they were not of the large kind. There was no cardiac disease. The liver was congested but not enlarged. The spleen was not enlarged and seemed natural on section. The bone-marrow was not examined.

(25) J. Löw and H. Popper (1908). Their second case was a woman, admitted into hospital with right hemiplegia of 14 days' duration. Spleen much enlarged. Red blood-cells 9,300,000. White cells 23,000. Haemoglobin above the normal. Death 5 days after admission. *Necropsy and microscopic examination*:—Thrombosis of the left common carotid artery and of the artery of the left Sylvian fossa, with consecutive softening in the left cerebral hemisphere. Chronic interstitial nephritis. The spleen was engorged with blood and showed increase of reticular tissue; the splenic pulp consisted chiefly of red blood-corpuscles and leucocytes; only remnants of the Malpighian corpuscles were left. The bone-marrow from the right thigh was examined. It was dark red in colour and full of dilated blood-vessels; there were only a few fat vesicles left; the cells consisted of numerous neutrophile and eosinophile myelocytes, fairly numerous neutrophile and eosinophile polymorphonuclear leucocytes, fewer small and large lymphocytes, erythroblasts (medium quantity), giant-cells and erythrocytes; the giant-cells, namely megakaryocytes and (fewer) myeloplaxes were relatively increased in number.

## APPENDIX B

### Specially Remarkable or Obscure Cases with Polycythaemia

(1) R. G. Hann (1908). (?) *Erythraemia of early life. Improvement in the general condition accompanied by increase of the polycythaemia.*—Girl, aet. 18. Enjoyed good health till 13 years old. Bodily development since then somewhat retarded. Menstruated twice when 15 years old, but never since. During the last two years suffered occasionally from severe abdominal pains of uncertain nature. Spleen extended three finger-breadths below the left costal margin. Liver not enlarged. Red blood-cells between 6 and 7 millions; haemoglobin 110 per cent. In this case an inherited syphilitic taint was suspected. In August, 1908, Dr. Hann kindly informed me that since January (when I had had the opportunity of studying the patient), under treatment by potassium iodide, iodide of iron, and occasionally tincture of perchloride of iron, the girl's general condition had decidedly improved, but the splenic enlargement remained unaltered and the polycythaemia had slightly increased (7,270,000 red cells on August 12). In regard to the increase of the polycythaemia accompanying improvement of the general condition compare Appendix B, Case 12.

(2) Nichamin (1907). *Erythraemia of early life.*—Young woman, aet. 20. Chronic cyanosis, polycythaemia, and splenomegaly. The splenomegaly dated from early childhood, and the cyanosis from the age of 13 years. She commenced to suffer from various haemorrhages when she was 15 years old. At 17 years she acquired malaria. Her sister had likewise enlargement of the spleen from childhood.

(3) Minkowski (1905). *Erythraemia of early life.*—Man, aet. 22. Remarkably cyanotic from early childhood. No heart disease. Polycythaemia. Splenomegaly. Came under notice for a cyst in the capsule of the right kidney, a most unusual condition, which was operated on successfully.

(4) M. Ascoli (1904). *Polycythaemia with splenomegaly (? toxaemic factor).*—A carpenter, aged 20 years. History of malaria and double otorrhoea. Cyanosis of face. Pigmentation of abdomen. Spleen somewhat enlarged. The urine showed a trace of albumin, excess of urobilin and some tube-casts. Blood: red cells 7,200,000; white cells 15,000 (of which eosinophiles constituted 20 per cent.); no erythroblasts seen; haemoglobin only 95 per cent. Improvement occurred whilst he was in the hospital. On one occasion arterial blood taken from the radial artery gave 6,100,000 red cells, whilst capillary blood from the lobe of the ear gave only 6,000,000 (could this be due to admixture of subcutaneous serum ?). Comparison with other cases seems to me to suggest a toxaemic factor in Ascoli's case.

(5) P. K. Pel (1907). *Toxic polycythaemia and haemoglobinuria.*—Man, aet. 33. Syphilis 11 years ago. Polycythaemia; 6 to 9 million red cells; haemoglobin-value 110 to 140 per cent. Repeated attacks of paroxysmal haemoglobinuria. Pel suggests that both the polycythaemia and the paroxysmal haemoglobinuria may have been of toxic origin.

(6) A. Fells (1908). *Toxic polycythaemia with chronic sulphonal poisoning and haematoporphyrinuria.*—A woman, aet. 37, who had been long resident in India, and had suffered from sunstroke and many attacks of fever. In 1906 she had intermittent pyuria with pyrexia. The blood-count showed polycythaemia (6,500,000 red cells) without leucocytosis. The urine became of a clear port-wine colour and was reported to contain 'urobilin', but Dr. Fells kindly informs me (August, 1908) that a subsequent careful investigation showed the red colour was due to haematoporphyrin. The woman had been accustomed to take sulphonal for years, though none had been prescribed during the nine months

prior to her death. No splenomegaly could be detected clinically: there was no post-mortem examination.

(7) Guinon, Rist and Simon (1904). *Acholuric jaundice and splenomegaly with temporary (toxaemic?) polycythaemia.*—Girl, aged 10 years. Chronic jaundice of variable degree with urobilinuria and chronic splenomegaly. Transitory cyanosis and polycythaemia accompanied exacerbation of the jaundice. Red blood-cells 6,000,000 to 7,600,000. Two or three months later the number of red cells fell to 4,000,000, and a year previously the count had given only 3,400,000. The resistance of the red cells to haemolysis was above the average. This case may certainly be compared in some respects to Hayem's chronic splenomegalic 'acholuric' jaundice (with oligocythaemia).

(8) M. Mosse (1907). *Acholuric jaundice (no bilirubin in the urine), splenomegaly with polycythaemia.*—A man, aet. 58, with chronic splenomegaly, urobilinuria and chronic acholuric jaundice. Red blood-cells 6,750,000 to 7,825,000; haemoglobin 100–110 per cent. Mosse compares his case in some respects to cases of splenomegalic polycythaemia (erythraemia), in other respects to the cases described by Hayem under the heading 'chronic infectious splenomegalic jaundice'. In Hayem's cases there was likewise urobilinuria (without bilirubinuria), but there was oligocythaemia instead of polycythaemia as in Mosse's case. Mosse's case may likewise be compared to the preceding one (No. 7).

(9) F. Dronke and C. A. Ewald (1892). *Polycythaemia from use of iron and arsenic.*—These authors in one case observed great polycythaemia following the long use of Levico water (which contains iron and arsenic). On November 23, 1891, the red cells were 5,120,000; on December 14, 5,300,000; on January 23, 1892, 8,400,000. This last count was carefully controlled by a second count and found to be correct. It is, however, noteworthy that with so remarkable a polycythaemia the haemoglobin-value was found to be only 85 per cent. of the normal.

(10) H. Neumann (1894). *Polycythaemic reaction (a form of 'blood crisis') following oligocythaemia.*—Man, aet. 57. Supposed to have Addison's disease, of acute onset, accompanied by great anaemia. Then a gradual improvement in the man's general condition followed, and the oligocythaemia gradually gave place to polycythaemia. Afterwards the number of red cells fell again to the normal. The count of erythrocytes gave 1,120,000 on April 15, 1885; 3,330,000 on June 8; 5,490,000 on July 24; 6,500,000 on October 1; 7,700,000 on January 8, 1886; 6,590,000 on January 26; and 5,500,000 on July 6. It is probable that when cases of anaemia from haemorrhage and other forms of anaemia improve with or without special treatment, the anaemia may occasionally give place to a temporary polycythaemia, as if the normal level had been overshot by the reactive effort of the blood-forming tissues.

(11) F. Geisböck (1905). *Case of (clinically) splenomegalic polycythaemia with low blood-pressure. Unsuccessful treatment by Röntgen rays.*—Man, aet. 51. Apparent recovery from severe jaundice. Then headache, giddiness, and loss of appetite and weight. Face somewhat cyanotic. Slight goitre. No disease of heart or lungs. Blood-pressure 100 to 110 mm. Hg. Liver and spleen enlarged. Occasional trace of albumin and a few tube-casts in the urine. Red blood-cells 9,100,000. White cells given as only 1,080. Haemoglobin-value 200 per cent. Venesection of 260 c.cm. scarcely relieved his headaches, nor did the application of Röntgen rays to the spleen improve his general condition. Carlsbad treatment had a better effect. Geisböck thought the case resembled some of those described by Türk.

(12) C. Begg and H. H. Bullmore (1905) and T. J. Horder (1908). *Case of (clinically) splenomegalic polycythaemia. Good results from inunction of*

*biniodide of mercury over the spleen and large doses of quinine. Afterwards good results from application of Röntgen rays to the spleen.* Woman, aged 47 years in 1904, when she was treated at Bath by Dr. C. Begg. Red blood-cells 6,850,000. White cells 11,300 (of which polymorphonuclears 77·3 per cent.). Haemoglobin-value 100 per cent. Poikilocytosis and polychromatophilia were well marked, especially the latter. No myelocytes were seen. About four normoblasts were counted to a thousand white cells. Diminution in the size of the spleen and subjective improvement undoubtedly accompanied the treatment by quinine and inunction with biniodide of mercury (the part being exposed to artificial heat). It may here be noted that up to the age of 30 years the patient had suffered from frequently recurring 'liver attacks' with vomiting; after that age the attacks recurred less frequently. In May, 1906, she was first seen by Dr. Horder, who has kindly given me notes of her further progress. The spleen was very large, but under treatment with Röntgen rays (Dr. Horder and Dr. Lewis Jones) it decidedly diminished in size. The patient's general condition likewise improved, although the number of red blood-cells (5,400,000 before the Röntgen treatment) increased simultaneously with the improvement. It seems possible, as Dr. Horder suggests, that in this case the polycythaemia was in some way 'compensatory'. It may be noted, however, that in Hann's case (Appendix B, 1), increase in the polycythaemia likewise accompanied improvement in the patient's general condition. Dr. Horder, who is shortly going to publish an account of his observations, tells me that the subcutaneous tuberculin test gave a negative result on three occasions.

(13) Münzer (1908).—*Erythrocytosis probably from blood-stasis not of cardiac origin. Obesity. Thyroid treatment.* The first case mentioned by Münzer was that of an obese man with extreme tendency to fall asleep. Cyanosis. Red blood-cells 9,800,000. No enlargement of spleen or liver. There was distension of the neck, which Münzer supposed was connected with substernal fat or goitre. Under thyroid treatment the man's weight fell from 103·0 to 89·3 kilograms and all his alarming symptoms disappeared.

(14) F. Geisböck (1905). *Polycythaemia with high blood-pressure treatment with iodothyrin.* Man, aet. 55, a bank-director, overworked and very excitable. Little enlargement of the heart; slight irregularities in the cardiac action. No albuminuria. 'Rush of blood' to the head at times. Erythrocytes 6,100,000. Haemoglobin-value 108 per cent. Blood-pressure 170 mm. Hg. Improvement after the use of iodothyrin. The blood-pressure fell to 120 mm. Hg.

(15) F. Geisböck (1905).—*Slight polycythaemia with chronic interstitial nephritis.* Man, aet. 51. Admitted with cerebral haemorrhage. Red face. Some enlargement of the heart. Arteriosclerosis. Albumin and tube-casts in the urine. Red blood-cells 5,700,000. Haemoglobin-value 104 per cent. Blood-pressure 250 mm. Hg. The necropsy showed decided, but not extreme, chronic interstitial nephritis.

(16) F. Geisböck (1905). *Polycythaemia with high blood-pressure and arteriosclerotic gangrene of the foot.* Man, aet. 64. History of hard work and some indulgence in alcoholic drink. Red blood-cells 10,400,000 to 11,320,000. Haemoglobin-value 156 per cent. Brachial blood-pressure 150–160 mm. Hg. Trace of albumin in the urine. Arteriosclerosis. Gangrene of the right foot. Amputation. The dorsalis pedis artery of the amputated foot was extremely sclerotic.

(17) F. Lommel (1908). *Polycythaemia with 'angina cruris' and commencing gangrene of the foot.* Man, aet. 47, thin. Severe pain and commencing gangrene in the right foot with absence of pulsation in the right anterior tibiali artery. Pirogoff's amputation was performed in 1903. In 1906 Lommel detected

a considerable polycythaemia (9,700,000 red cells and 150 per cent. haemoglobin-value). There was clubbing of the fingers.

(18) F. Schupfer (1908). *Polycythaemia and chronic cyanosis following the operation of splenectomy for splenomegaly in Banti's disease.* In a man, aet. 42, the enlarged spleen was removed for supposed Banti's disease, and the progress of the case was followed for 3 years. The man's general health was improved, and the liver, which was enlarged before the operation, returned to its normal size. But polycythaemia and chronic cyanosis gradually developed. The red blood-cells 3 years after the operation were 6,270,000, whilst before the operation they had been only 2,880,000 to 4,920,000 in the cubic millimetre.

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# ON HYSTERICAL PAROXYSMAL OEDEMA[1]

By F. H. EDGEWORTH

THIS paper is an attempt to differentiate, from the large and indiscriminate class of cases sometimes called 'angio-neurotic oedema', a group which is of hysterical origin, and which is characterized by the repeated occurrence of transitory oedema affecting 'geometrical' or 'segmental' areas of the body-surface, associated in some cases with disturbance of sensation hysterical in type.

The following cases are recorded in support of this opinion, and I have appended others which show that no marked line of division can be drawn between hysterical paroxysmal oedema and the well-recognized hysterical chronic oedema of Sydenham and Charcot.

*Case I.* T. R. V., aged 24, a plumber by trade, came to the Bristol Royal Infirmary on June 9, 1896, complaining of swelling of the left arm and left foot. On inquiry, the following facts were obtained. There was no family history of any physical trouble similar to that which had affected the patient for the previous eleven years. The phenomena were as follows:—he might go to bed perfectly well and wake in the morning with a swollen foot, the swelling being so great that he could not put his boot on. This would last all day and gradually subside. The attacks were of fairly frequent occurrence, a month rarely passed without one, and of late the interval between successive attacks had gradually lessened until, as a rule, it was not greater than a week. Any part of the body might be affected, sometimes the foot or leg, sometimes the hand and arm, often the face, rarely the trunk. If the upper part of the face were affected the patient could not see with the corresponding eye for several hours owing to the swelling of the lids. In general not more than one part of the body was affected at the same time; if two at once they were usually on the same side. He had a burning, itching feeling in the slightly red, swollen area, and this area could not be indented by the pressure of a finger until the attack began to subside. But for these attacks he was in the best of health, and could not remember ever having had any illness.

The patient looked a most healthy young man. No evidence of disease in the chest, abdomen, or kidneys could be detected. The parts affected by the oedema were the left forearm and the left foot. The left foot was uniformly swollen up to the level of the ankle, the swelling having precisely the same limits as a boot; it was slightly red, felt a little hot, and could be indented by the pressure of the finger (the patient said the attack was subsiding). The left forearm was similarly affected, from two inches above the wrist to the level of the elbow; the oedema extended right round the limb, and had a circular margin above and below. In both foot and forearm the surface of the skin was raised by the

[1] An account of three of these cases was read before the Bristol Medico-Chirurgical Society in 1898; the whole paper was part of a thesis for the degree of M.D. Cantab. in 1908.

oedema to the height of about a quarter of an inch above its normal level, and the oedematous area subsided to the healthy skin in the space of about half an inch. No anaesthesia, thermo-anaesthesia, or analgesia of the skin were present in either the affected or the normal parts. No hysterogenic zones were present. The muscular system was normal, as were also the skin reflexes and tendon-jerks.

The patient was seen during several subsequent attacks. Thus, on June 21, he came with a swelling of the right hand which had been present for nineteen hours. There was oedema of the hand and wrist up to two inches above the level of the joint, invading the whole circumference of the limb and having a circular upper margin. The most interesting attack was witnessed on June 26; it began with swelling of the upper lip and gradually spread to the lower lip and left side of the face. It was found that the whole of the lower lip, the left half of the upper lip, and the left side of the face were swollen; the swelling was less in the upper part of the cheek and the eyelids were not

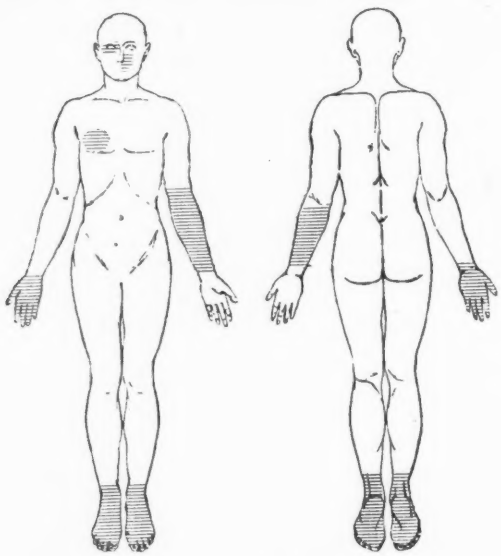

FIG. 1.[1] (Case I.)

affected. The surface of the left side of the face, though not hyperaemic, felt a little hotter to the touch than that of the opposite side. The mucous membrane of the left cheek within the month presented numerous blebs varying in size from a pea to a sixpenny-piece and filled with clear yellow serum. (On inquiry the patient said he always had blebs inside the mouth when the cheek was affected.) Other attacks were also seen, occurring in the upper part of the right side of the face and almost closing the eye, in the right foot, in the right hand, and in the right breast. The last had a more or less circular form and measured five inches across. No disturbances of sensation were found in any of the attacks.

Whilst the patient was under observation the attacks became less acute and occurred at longer intervals. On August 21 he had not had any attacks for four weeks and ceased to attend. He was subsequently seen in April, 1899—nearly three years later—and said that the disease had not recurred since

[1] The figures give the distribution of the oedema only.

August, 1896. At this time he complained of giddiness, and was found to have aortic valvular disease, from which he died six months later.

*Case II.* H. W., aged 32, bootmaker, came to the Infirmary on February 1, 1899, complaining that for ten days previously he had been suffering from pain in the head and swellings in various parts of the body. The left foot was the first part affected—the whole of the foot (with the exception of the toes) up to the level of the ankle became swollen. The next day the right foot was similarly affected; on the following day the left hand with exception of the fingers, and on the succeeding one the right hand in a similar manner. After an interval of one day the skin round the left eye became so swollen that he could not see, and on the following day the right eye was similarly affected. On the day before he came to the Infirmary the upper and lower lips on both sides swelled,

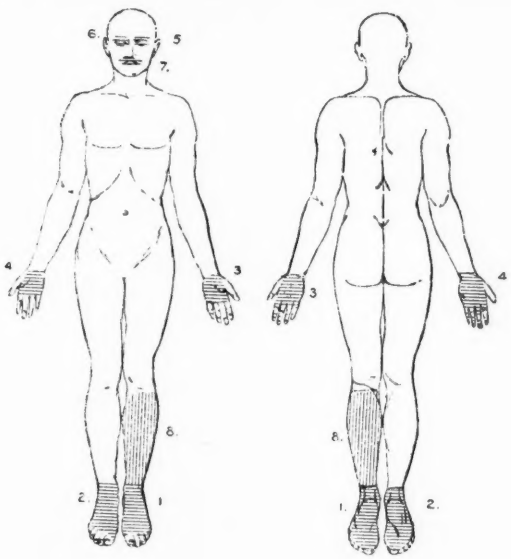


FIG. 2. (Case II.)

without any blebs on the mucous surface. Each attack lasted from ten to twelve hours, and the swollen part itched a little. On examination, the viscera, movement, sensation, tendon-jerks, and skin reflexes were found to be normal, and no oedematous areas could be seen.

On February 28 he came again, and said that no attack had occurred during the week, but that one had begun three hours previously in the left leg. It was found that the subcutaneous tissues of the left leg, from the level of the ankle to two inches below the knee, were evenly swollen, so that the surface was raised about $\frac{1}{4}$ inch above its normal level. The upper and lower borders of the oedematous area were circular, at right angles to the long axis of the limb, and fairly abrupt. The skin was not hyperaemic, though it felt a little hot, and it could not be indented by the firm pressure of a finger. No defects of sensation were discovered. No further attacks occurred during the month that he was under treatment.

*Case III.* Louisa H., aged 18, was admitted to the Infirmary on August 23, 1903. She said that for a year past the right hand had swelled two or three

times a week; it first ached and felt numb, and, in about a couple of hours, swelled to such an extent that she could not bend it at wrist- or finger-joints. The swelling lasted ten or twelve hours. During the month previous to admission she had also had swellings of the face; these began with pains in the eyelids, followed by such extensive swelling that she could not see with either eye. The first attack began at 10.45 p.m., by 12 p.m. she could not see, next morning it was gone; the second attack began at 3 p.m., was at its height at 5 p.m., and was not quite over in the morning. Each attack affected both eyes.

On admission, no oedema was present. The girl was anaemic, cardiac action was rapid, and there was a pulmonary haemic bruit. The lungs, abdomen, and urine were normal. Examination of the blood showed 60% haemoglobin, 4,000,000 red corpuscles, and 20,000 white corpuscles per c. mm.

On September 4 the right hand was found to be oedematous, very white in appearance, and cold to the touch. The swelling affected the fingers, thumb,

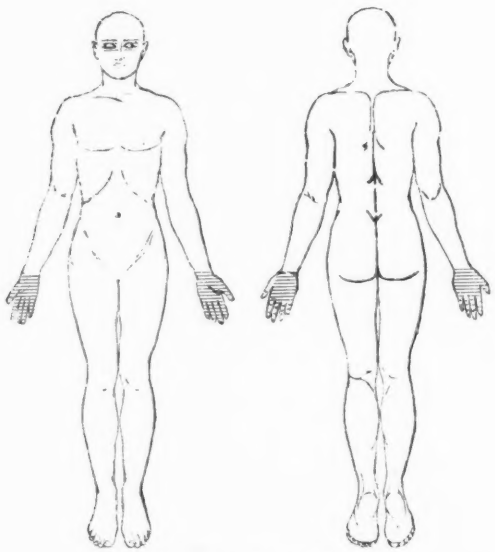

FIG. 3. (Case III.)

back and front of hand, and had a circular abrupt upper margin; it did not pit on pressure and subsided by the evening. On September 7 there was a precisely similar attack in the left hand. Up to September 23 no more attacks had occurred, and the patient went home.

*Case IV.* E. L., aged 22, a tailor's presser, came to the Infirmary on November 6, 1896, complaining of swelling of the right hand. He said his illness had begun twelve months previously, with a swelling in the sole of the right foot, which lasted a few hours only. Since then scarcely a week had gone by without one of the hands, or hand and forearm, becoming affected. As a rule there was a little itching of the skin before the swelling occurred; this lasted about twenty-four hours, and then gradually subsided. Otherwise he enjoyed good health.

The patient was a flaxen-haired, healthy-looking young man. The chest, abdomen, and urine were normal. The right hand, back and front, including fingers and thumb, was oedematous up to the level of the wrist with a circular

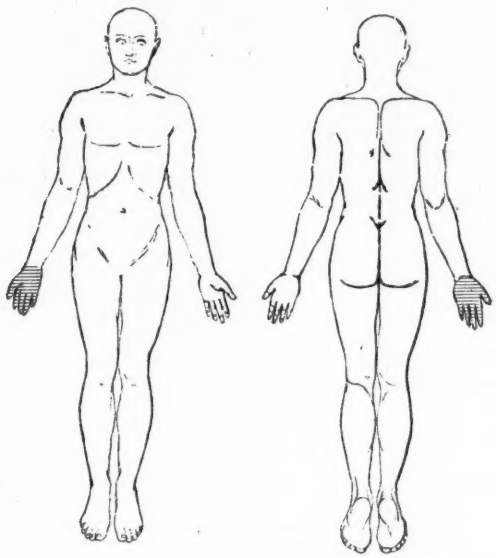

FIG. 4. (Case IV.)

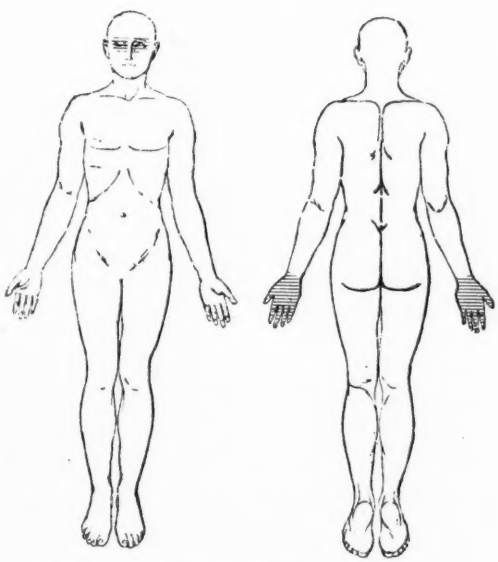

FIG. 5. (Case V.)

upper margin; the affected area could scarcely be indented by the firm pressure of a finger. The skin was not hyperaemic. The skin affected by the oedema, and for two inches above (i.e. the area which could be covered by a high-buttoned glove), was partially anaesthetic to touch, heat, and cold, and was totally analgesic to the prick of a pin. The nervous system was otherwise normal. Sensation elsewhere was perfect, movements were unimpaired, skin-reflexes and tendon-jerks normal. No hysterogenic zones were present.

No further attacks took place during the month he was under treatment, and when inquiry was made a year later the patient said he had had no recurrence of the disease.

*Case V.* Rose H., aged 34, came to the Infirmary on September 29, 1899, complaining of swellings in the arms and face during the previous fortnight. Each attack had lasted about forty-eight hours, and the parts affected had been either the back of one of the hands or the eyelids on one or other side, the swelling being so great that she could scarcely see. She had no pain, only a burning feeling in the swollen part. The swelling in the left hand, for which she came, had begun on the previous evening.

It was found that the dorsum of the left hand from the level of the wrist to the roots of the thumb and fingers was oedematous, slightly red and hot, and admitted of slight pitting on firm pressure. The whole hand—back and front, thumb and fingers—was partially anaesthetic for sensations of touch and heat, and partially analgesic to the prick of a pin. Two days later the swelling and affection of sensation had disappeared.

No further attacks occurred up to November 10, when she attended for the last time.

*Case VI.* Mrs. A. B., aged 37, came to the Infirmary on February 1, 1898, complaining that for the previous fortnight she had been troubled by swelling of the left arm at night. She would go to bed quite well, and be awakened between 2 and 3 a.m. by a numb pain in the left arm, and find, on lighting a candle, that it was swollen from the elbow-joint to the wrist-joint. It was also slightly hot and felt heavy. After a time she would fall asleep again, and wake in the morning with but little trace of the swelling left. This occurred two or three times a week.

On examination, it was found that in the left arm, from two inches below the shoulder-joint to two inches above the elbow, with sharply defined circular upper and lower margins, there was almost complete analgesia and thermo-anaesthesia, whilst tactile sensibility was normal. This analgesia and thermo-anaesthesia were removed by hypnotic suggestion. It was also suggested to her that no more attacks of swelling should take place, and during the subsequent two months that she attended as an out-patient none occurred.

*Case VII.* Annie F., aged 17, came to the Infirmary on April 27, 1900, complaining of a swelling of the right hand which had begun four days previously. She had had no pain either before or after the swelling had taken place, and complained only of the mechanical inconvenience caused thereby. It was found that the right hand was affected by a smooth, scarcely pitting oedema on both surfaces, though it was more marked on the dorsum, where the skin was raised to about $\frac{3}{4}$ inch above its usual level. The swelling had a sharply defined circular upper margin at the level of the wrist and extended down to the proximal interphalangeal joints of the thumb and fingers. The colour of the skin was purplish; on slight pressure this faded, and slowly returned on relaxation of the pressure. The affected hand felt a little colder than the other. There was no disturbance of sensation either in the right hand or elsewhere.

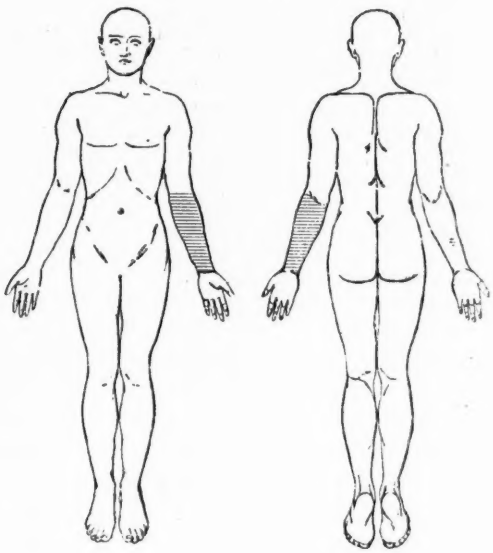

FIG. 6. (Case VI.)

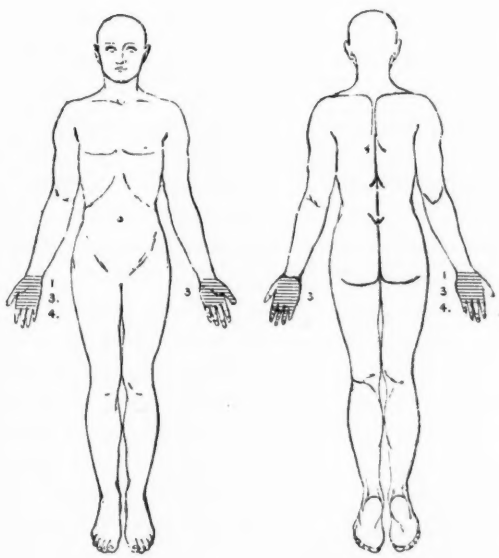


FIG. 7. (Case VII.)

The fields of vision were contracted, and the plantar reflexes absent. Nothing else abnormal was discovered.

The patient remained in the same condition until July 23, when, three days after being made an in-patient, the oedema disappeared in the course of a night. It had lasted eleven weeks. The patient was then sent out. Five days later the condition recurred and persisted, in spite of the patient being taken in, until November 28, i.e. for a period of thirteen weeks. This second attack differed from the first one in that (1) the oedema reached about half-way up the forearm, and gradually diminished, without any definite upper margin; (2) the oedematous area was tender on pressure. A third attack lasted from December 13 to December 15, and affected both hands. In each hand the oedema extended from the proximal phalangeal joints of thumb and fingers to two inches above the wrist, and had a circular upper margin. There was no pain on pressure. A fourth attack lasted five days, from December 18 to December 23, and affected the right hand only up to the wrist. Each attack began and ended during the night. No anaesthesia or analgesia occurred, but the contraction of the fields of vision persisted during the whole time that the patient was under observation.

On analysis of these cases it is evident that all presented the features of a subcutaneous oedema, of fairly sudden onset, raising the surface of the skin from $\frac{1}{4}$ inch to $\frac{3}{4}$ inch above its ordinary level. The whole area became affected, and, as a rule, uniformly affected at the same time—the oedema was not a spreading one. The surface of the skin was generally natural in colour, but in some cases was hyperaemic, or white and cold, or purplish. The oedema was firm and non-pitting when at its height; during its subsidence it became softer. No bullae formed on the skin. Blebs containing a clear yellow serum were found in one case when the oedema affected the mucous membrane of the cheek. The oedematous area was (in almost all cases) sharply marked off from the adjacent normal surface by an abrupt edge.

The occurrence of the oedema generally caused no pain; the mechanical inconvenience was the chief cause of complaint. In some cases there was a sensation of itching or burning with the onset of the attack.

The duration of each attack varied from eight hours to two days, except in the last recorded case, where, in one attack, it amounted to thirteen weeks.

The areas affected by the oedema were not those supplied by any branch or branches of cranial or spinal nerves, nor those supplied by cranial or spinal nerve-roots ('segmental' areas of Thornburn, Head, and Sherrington). They corresponded with natural divisions of the body, e.g. mamma; or with areas covered by articles of clothing, e.g. stocking, sock, glove—that is, with the areas called 'geometrical' or 'segmental' by writers on hysterical phenomena.

In three of the seven cases recorded, disturbances of sensation—partial or complete loss of sensibility to touch, painful or thermic stimuli—coexisted with the attacks of oedema. In none of the cases could this loss be attributed to the mechanical effects of the oedema, as its area never corresponded exactly to that of the oedematous swelling. The areas over which this loss of sensibility occurred were also of the 'geometrical' type, though differing from those of the oedema in their greater extent. In one case the area of loss of sensi-

bility did not coincide with that of the oedema, though on the same limb. In one case there was no alteration in the sensibility of the skin, but the fields of vision were contracted.

There was no difference, in regard to the extent or nature of the oedema, between the cases in which disturbances of sensibility occurred and those in which they did not occur. In both classes the oedema affected 'geometrical' areas, did not spread at its margins, which were abrupt, and was, when at its height, a firm one. The peculiar distribution of the oedema in these cases, and its association, in some, with disturbances of sensibility, suggest that it was of hysterical origin.

This conclusion is supported by comparison of the condition with the hysterical chronic oedema first described by Sydenham in 1682, and subsequently by Charcot and his pupils. This affection is rarely found as an isolated phenomenon; it is generally superimposed on some other hysterical manifestation, such as an arthralgia, paralysis, or contracture. It is of variable aspect, either white-pink or bluish in colour, hard, and invading the whole circumference of the part affected. It is generally accompanied by disturbances of sensibility, which are apt to take the form of hyperaesthesia in arthralgias, anaesthesia and thermo-anaesthesia when superimposed on a paralysis or contracture. It is of variable duration, but generally lasts a long time, e.g. two years, and is described as being 'une lésion fort tenace, et dont la gravité se mesure à celle de la manifestation principale'. It is subject to fluctuations in intensity as long as it persists, and when it disappears does so suddenly.

The similarities between paroxysmal and chronic hysterical oedema lie in the 'geometrical' distribution, in the firmness of the oedema, and in the frequently associated disturbances of sensibility. The differences are that in the paroxysmal variety—if one may judge from an experience of only seven cases—the phenomenon is not usually superimposed on some other manifestation, and is of transitory, and often of a recurring, nature. Cases, however, occur which are transitional between the two varieties, e.g. in the last case the attacks varied in duration from two days to thirteen weeks. Thus it is easy to distinguish paroxysmal from chronic hysterical oedema. It is however difficult, and impossible at first in some cases, to distinguish between the former condition and that which is sometimes called 'angio-neurotic' oedema.

This disease was first described by Milton in 1876, and subsequently by Quincke in 1882, but did not attract much attention until Osler, in 1888, recorded its occurrence in twenty-two members of a family, extending over five generations. Since then many cases have been reported under various names, e.g. 'giant urticaria', 'Quincke's oedema,' 'neuritic oedema,' 'angio-neurotic oedema,' 'acute recurrent oedema,' 'segmental oedema,' 'acute circumscribed oedema.'

This disease—which I shall call 'Quincke's oedema', for all its essential features were described by Quincke—is often hereditary. The taint passes through both males and females, who may or may not be themselves affected.

Both sexes suffer. It may begin in childhood or in adult life. It consists of recurrent attacks of circumscribed oedema in any part of the body, especially the face and extremities. The mucous membranes may be affected—mouth, palate, pharynx and larynx, and there may be colic, vomiting, and diarrhoea—probably due to oedema of the gastro-intestinal wall. Oedema of the larynx may be a cause of suffocation and death. The areas of skin affected are very various in size, but, as far as I can learn from reported cases, are not 'geometrical' in shape.

This affection is closely allied to the disease which was first described by Henoch in 1874, and which is sometimes called 'Henoch's purpura'. Our knowledge of its characteristics was much extended by Osler's investigations. The features common to Quincke's oedema and 'Henoch's erythema' (as perhaps it might be called) are the presence of a cutaneous lesion associated with gastro-intestinal crises, and the liability to frequent recurrence. The differences are that in the latter disease arthritis and enlargement of the spleen may occur, the lesions are more frequently of a haemorrhagic character, the hereditary tendency is absent, and the age of onset is generally earlier. In these two diseases there is a recurring lesion of the vessels resulting in transudation of either plasma or blood.

The cause of the lesions has not yet been determined. Quincke put forward the theory that the affection is a vaso-motor neurosis, owing to which the permeability of the vessel-wall is suddenly increased. This theory has been adopted by many subsequent writers, and is assumed in the name 'angio-neurotic oedema'. There is, however, very little evidence in its favour. The areas of the cutaneous lesions do not harmonize with the territories of either nerve-roots or peripheral nerves, and the wide distribution of the lesions suggests some change in the blood.

In regard to this point it is to be remarked that Sir A. E. Wright has stated that urticaria, chilblains, oedema, and spontaneous haemorrhages may be due to, or associated with, deficient coagulability of the blood. He remarks that 'the association of a defect of blood coagulability with diarrhoea may also be inferred from Osler's observations on the frequent association of diarrhoea and vomiting with cases of morbus maculosus Werlhofii, i.e. with a disease which is plainly associated with a serious defect of blood coagulability'. The cause of 'Quincke's oedema' and 'Henoch's erythema' may thus be a recurring deficiency in the calcium content of the blood.

The diagnosis between Quincke's oedema and the hysterical paroxysmal oedema depends on recognition of the extent and form of the recurring firm oedema, and of its associated phenomena. In hysterical oedema the area affected is a 'geometrical' one, its edges are abrupt, and the affection is often accompanied by disturbances of sensibility, but not by gastro-intestinal crises.

Diagnosis would be impossible if the only phenomenon of a first attack were oedema of the face, e.g. eyelids or lips. One would have to wait until other skin-areas were affected or until visceral manifestations occurred.

I may sum up the foregoing by saying that the evidence recorded suggests that cases of paroxysmal oedema may be divided into two categories, those of Quincke's oedema and those of hysterical origin. The former are allied to Henoch's erythema, the latter to hysterical chronic oedema. The former are probably due to some blood-change, the latter to some disturbance in the central nervous system.

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# THE VENOUS PULSE IN PAROXYSMAL TACHYCARDIA

By JOHN COWAN, DAVID McDONALD, and ROBERT I. BINNING

There has been much discussion of recent years as to the nature of those attacks of rapid cardiac action which are usually described as Paroxysmal Tachycardia. There is a general consensus of opinion that they are due to frequently recurring extra-systoles, in some instances of nodal rhythm, in others originating above the ventricle, in sinus, auricle, or sino-auricular node. The accompanying tracings, which we obtained from two patients suffering from

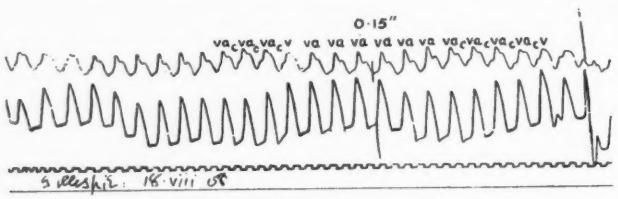


Fig. 1. Case I. Venous Pulse. P. R. 172.

this complaint, show that a normal auriculo-ventricular rhythm was present, so that our cases belong to the second group.

The first patient, a man of 40 years of age, remained in hospital for several months, during which he had some twenty attacks of varying duration. Tracings were obtained on many occasions and were always similar in

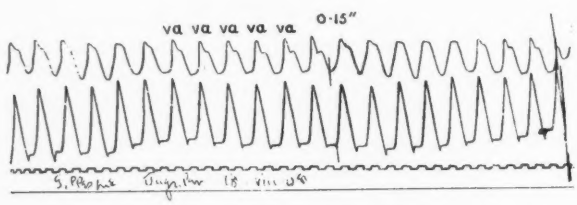


Fig. 2. Case I. Venous Pulse. P. R. 172.

character. The double wave shown in Fig. 2 was the usual form. The wave '*a*' is seen to occur 0·15 sec. before the radial upstroke, and as the radial upstroke only occurs 0·1 sec. after the commencement of the ventricular systole, as shown in Fig. 3, '*a*' must precede the ventricular systole and can only be due to auricular contraction. The wave '*v*', judged by similar tests, is evidently post-carotid in rhythm, i.e. the usual '*v*' wave.

[Q. J. M., Jan., 1909.]

In Fig. 1 the carotid wave '*c*' can sometimes be seen, and the *a–c* interval is rather less in duration than the normal, 0·2 sec. Figs. 4 and 5 show normal tracings taken between the attacks.

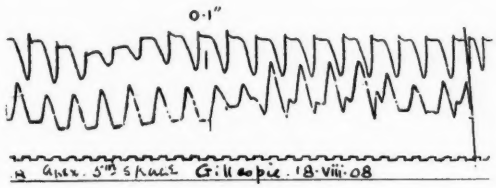


FIG. 3. Case I. Apex Impulse. P. R. 172.

It seems clear that in this case the auricle and ventricle contracted during the tachycardia in their normal sequence, while, as might be expected, the *a–c*

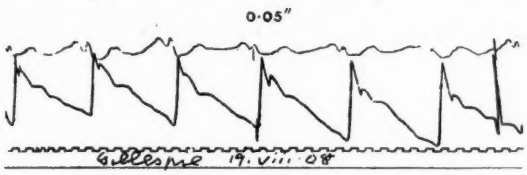


FIG. 4. Case I. Venous Pulse. P. R. 52.

interval is slightly shortened. The marked depression '*x*' indicates vigorous auricular action.

The commencement and the end of these attacks was instantaneous, but we

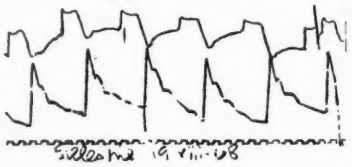


FIG. 5. Case I. Apex Impulse. P. R. 57.

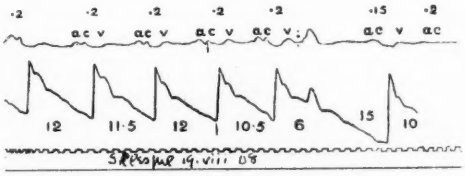


FIG. 6. Case I. Venous Pulse.

were never fortunate enough to obtain tracings during the transition. The pulse was practically always regular during his residence, but a few isolated

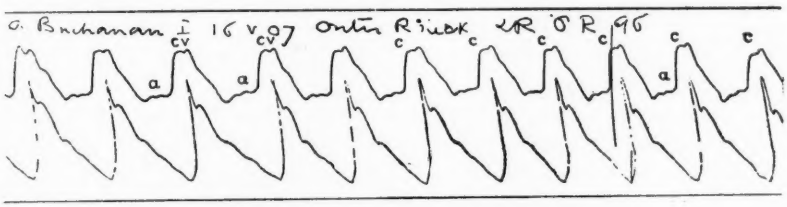


FIG. 7. Case II. Venous Pulse. P. R. 96.

extra-systoles, less than a dozen in all, were noticed to occur at times. Fig. 6 shows that one at least was infra-nodal in origin.

The patient in the second case was aged 38, and died shortly after the second attack which we observed. The tracings are less satisfactory, as a time-marker was not available, and in Fig. 8 the reference marks were lost. But

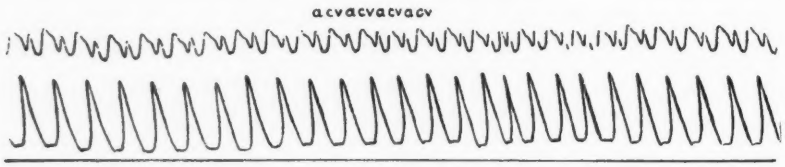


FIG. 8. Case II. Venous Pulse. P. R. 180.

in this case these marks are of little importance, as the patient suffered from well-marked tricuspid incompetence as well as double aortic disease, and the double wave '*cv*' in Fig. 8 can hardly be other than the '*cv*' wave in Fig. 7. '*a*' in both tracings must then be due to auricular contraction.

# THE EFFECT OF THE ADMINISTRATION OF CALCIUM SALTS AND OF CITRIC ACID ON THE CALCIUM CONTENT AND COAGULATION TIME OF THE BLOOD[1]

By T. ADDIS

(From the Laboratory of Physiology, University of Edinburgh)

In 1893 A. E. Wright published the first of a series of papers on the curative effect of Calcium Salts in certain pathological conditions, which were said to be associated with a diminished coagulability of the blood. Experiments with his coagulometer showed long coagulation times, which became very considerably reduced after the administration of calcium by the mouth. In several of these papers results are quoted to prove that in healthy people calcium will diminish the coagulation time, and that citric acid has the opposite effect. Thus a coagulation time of $5\frac{1}{4}$ minutes is reduced to $1\frac{3}{4}$ minutes twenty-four hours after taking thirty grains of calcium chloride. In 1905, with a modification of the original method, he gives similar results, the time within an hour after calcium being usually reduced to a half or a quarter of the time before calcium.

The general idea underlying Wright's work on this subject, although it is nowhere quite clearly stated, is that the administration of calcium leads to an increase of calcium in the blood, and that this increased amount of calcium induces more rapid coagulation. Finding from experiments on oxalated blood that the addition of increasing quantities of calcium diminished the coagulation time up to a certain point, but that after that point was reached coagulation took longer, he referred those cases in which a long coagulation time followed the giving of calcium to the absorption of an excess of the salt. He then devised a method of estimating the quantity of calcium in the blood in terms of the minimum concentration of ammonium oxalate solution necessary to keep the blood from coagulating. He demonstrated by this method that the administration of calcium is followed by an increase in the quantity of calcium in the blood. He was, however, unable to show any constant relation between the quantity of calcium and the coagulation time, and concludes that 'the content of the blood in lime salts as estimated by this method is, in fact, far from being an index of its coagulability'. These experiments are of the greatest interest and importance, especially from the point of view of

[1] The expenses of this investigation were defrayed by the Earl of Moray Fund of the University of Edinburgh.

therapeutics, and have attracted a great deal of attention. When, therefore, I succeeded in constructing a coagulometer which I had reason to believe gave reliable results, I proceeded to repeat Wright's experiments.

At that time Blair Bell had just published his method of estimating the calcium content of the blood, and after having made myself familiar with its use, I tested it, and found it sufficiently accurate. I therefore employed it in determining the relation between the calcium content and the coagulability of the blood. As my results in connexion with the effect on the coagulation time are at variance with those of Wright, it will be necessary to give a short description of the apparatus used and to discuss the differences between the two coagulometers. After giving the reasons for relying on Blair Bell's calcimeter, the results of calcium and citric acid on the coagulation time and on the calcium content as determined by these methods will be detailed. I am greatly indebted to Dr. J. S. Fowler for very valuable advice and criticism, and to Sir Thomas R. Fraser, Dr. R. W. Philip, and Dr. A. Bruce for permission to try the effect of calcium on convalescent patients in their wards.

## The Method of Estimating the Coagulation Time of the Blood.

A full description of the following method appears elsewhere, and I shall only give such a description as is necessary to indicate its mode of action. A drop of blood hangs from the end of a truncated glass cone similar to that used in Brodie and Russell's method. The cone is fitted into a small box (Bogg's modification of Brodie and Russell's apparatus) which is full of mineral oil, and by means of a fine nozzle a stream of oil from a reservoir is directed tangentially against the edge of the drop. The result of this is that a smooth, continuous, quickly flowing movement is induced in the corpuscles, although the drop itself remains stationary. This movement is observed under the low power of a microscope. The oil in its passage from the reservoir passes in a flexible metal tube through a water-bath kept at a constant temperature by means of Schäfer's gas thermostat, or, where gas is not available, by Gibson's electrical thermostat. Immediately after it has passed through the nozzle into the box and against the drop of blood, it impinges on the bulb of a fine thermometer, and the temperature of the oil immediately surrounding the blood can be read off. By these means an absolutely constant temperature can be indefinitely maintained. The coagulation time is measured from the moment when the finger is pricked to the time at which the flow of the corpuscles ceases. This occurs fairly suddenly, and is due to the formation of a fibrinous network throughout the drop which gives a laminated appearance just before the flow stops.

The process of coagulation in the apparatus is fairly comparable to that which occurs within a blood-vessel on account of the presence of a foreign body. Oil is neutral as regards coagulation and represents the intact endothelial lining

of the vessel. In both cases coagulation occurs on account of the injury done to the flowing blood by its friction against a foreign body (represented in the apparatus by the end of a glass cone). The main difference is that the blood in the apparatus has passed through the tissues of a wound, but the effect of this is slight, for I found, when all other causes of coagulation were excluded by keeping the blood immediately after it leaves the wound surrounded on all sides by oil, that it took as long as 80 minutes to coagulate, while in the apparatus under the same conditions with the addition of friction against the glass cone it took 7½ minutes.

The greatest advantage of the method is that the temperature can be kept absolutely constant in comparative observations. In none of the others is this the case. Where provision is made for this purpose it is inadequate, and several of the authors of methods appear to hold that the variations of temperature which occur in rooms and laboratories may be neglected. This is very far from being the case, as may be seen from the chart on p. 152, in which the coagulation curve is seen to fall and rise with variations in the room temperature. These times were taken by McGowan's method. The author does not recommend its use for accurate work without the addition of some means of keeping a constant temperature.

Similar variations are met with in the use of other coagulometers, and have led Vierordt, Bürker, and Coleman to the conclusion that there are regular daily variations in the coagulability of the blood. These are in reality, however, only variations due to the complicating effects of temperature changes and of other fallacies inherent in the different methods used. I found with my method that the time remained remarkably constant when the temperature was kept constant. The slight irregular variations which sometimes occurred were due to want of accuracy in picking up the proper size of the drop with the glass cone, and to an occasional indefiniteness in the end-point. The following results taken with this method show how temperature changes within the range of room temperature affect the coagulation time:—

| *Temperature.* °C. | *Coagulation Time.* min. sec. |
|---|---|
| 10·25 | = 21 30 |
| 12·25 | = 16 30 |
| 13·5 | = 14 32 |
| 14·5 | = 12 58 |
| 15·5 | = 11 46 |
| 16·5 | = 10 10 |
| 17·5 | = 8 27 |
| 18·5 | = 7 34 |
| 19·5 | = 6 2 |
| 20·5 | = 5 22 |

It is obvious from the above figures that even slight differences of temperature are sufficient to invalidate the results of comparative observations.

Wright's method has undergone several slight modifications. In its latest

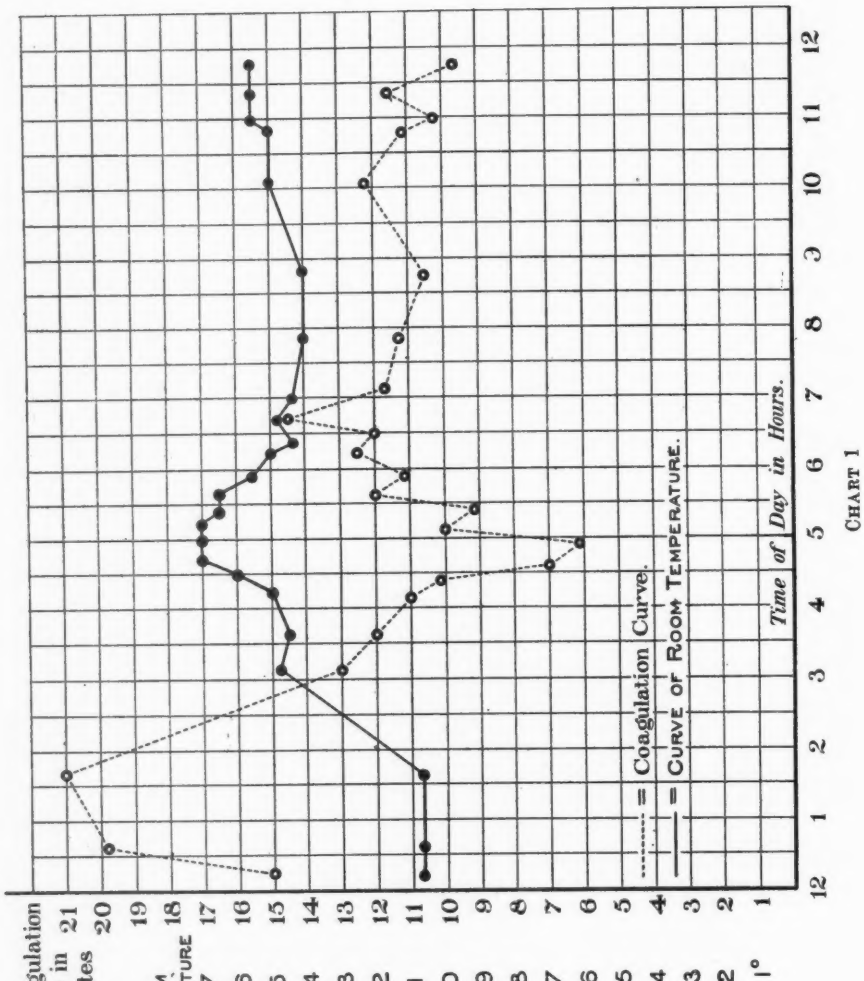
Coagulation Time in Minutes
Room Temperature °C
Time of Day in Hours.
= Coagulation Curve.
= Curve of Room Temperature.

CHART 1

form it consists of a series of capillary glass tubes accurately graduated by a most ingenious use of throttle pipettes and mercury. When filled with blood they are placed in a water-bath at 37° C., and at intervals one after the other is taken out and blown on to filter-paper until a thread or mass of fibrin can be seen in the expressed blood. The coagulation time is the time elapsing between pricking the finger and the first appearance of fibrin. In this method there is no adequate provision for the maintenance of a constant temperature. There are no means of maintaining the water in the bath at 37° C. except by adding more hot water, which is a very inaccurate method. The time required for an observation is, however, very short, and the very slight fall from 37° C. in the time would not introduce a serious error. More important is the fact that it is very difficult to keep the time before and after immersion in the water-bath constant. With times of 15, 30, and 45 seconds, which Wright quotes, the amount of time taken to fill and blow out the tube would obviously be a very important factor, for the longer it is exposed to room temperature the longer will the coagulation time be.

But the most important fallacy in his method is connected with the end-point he adopts. The blood is said to be coagulated when a thread of fibrin is seen. Now Buckmaster has noted that when a drop of blood is touched with a fine iridium-tipped needle a thread of fibrin several millimetres long can often be demonstrated within 10 seconds of the flow of the blood from the puncture. He cites this as showing that a certain degree of coagulation is present in the blood as soon as it is shed. I have very often seen the same thing on withdrawing the glass cone used in Brodie and Russell's method from a drop of blood on the finger. There are no other signs of coagulation, and the same drop will probably give a coagulation time of 7 or 8 minutes. A possible explanation of this is to be found in Mann's *Chemistry of the Proteids* (1906). On page 382 he says, 'Ramsden, in a paper not yet published, states that fibrinogen solutions, free from fibrin ferment, can be made to yield "mechanical surface aggregates" indistinguishable from typical fibrin, and that fibrinogen, mechanically-produced fibrin, and ferment-produced fibrin have the same heat coagulation temperature, 53°–58°.' When the blood is blown out of one of Wright's tubes and the fine glass tube is slowly withdrawn from the drop the conditions are present under which this phenomenon occurs. Whether it is mechanically-produced fibrin or not is immaterial, for even if it is true ferment-produced fibrin, it is a phenomenon which is due to the chance concomitance of external physical conditions, and one which bears no relation to the coagulation of the blood as a whole. I think that this is the explanation of the great reductions of the coagulation time after the administration of calcium which have been recorded by the use of Wright's method. I was unable to obtain any lessening of the time after calcium, when I took care to avoid this fallacy by not touching the expressed drop with the capillary tube.

The following are the opinions of those who have worked with Wright's method. Murphy and Gould failed to obtain any result in 15 per cent. of their

observations. Ross gives fourteen cases of a certain type of headache, in which he found a delayed coagulation time which was very greatly diminished by calcium. Coleman preferred Brodie and Russell's method. Solis-Cohen failed to obtain any reliable results. Douglas used the method in his work on the coagulation time of normal, pregnant, and eclampsic women, and appears to have been satisfied with the method. Nias showed that strontium as well as calcium salts are capable of diminishing the coagulation time, and considers that the method is sufficiently accurate for this purpose. Hinman and Sladen conclude that 'the pathological differences and those dependent on technique, in this method, are of about the same relative value, which must confuse the results'. Turner made over 1000 observations on healthy and on epileptic persons, and thinks the method a good one. His average time was 160 seconds, and he says that he often found differences of 120 seconds in blood taken from punctures made within a few minutes of each other in the same individual. These differences, however, he attributed to rapid variations in the coagulability of the blood, and not to any fallacy connected with the apparatus.

### The Method of Estimating the Quantity of Calcium Salts in the Blood.

In 1907 Blair Bell published the details of an extremely delicate and ingenious method of estimating the amount of calcium in a single drop of blood. There was before no method which did not require a very much larger quantity of blood than is ever available clinically, with the exception of Wright's, which, however, was only used to obtain a rough indication of considerable changes in the quantity of calcium. Bell's method consists of the accurate measurement by volume in a special pipette of 100 cm. of freshly-drawn blood. This is mixed with a known quantity of oxalic acid, and after an interval acetic acid and glycerine are added. After further dilution with distilled water a drop of the mixture is placed on a Thoma haemocytometer plate and the crystals of calcium oxalate are counted. When there is one crystal in each square the calcium index is 1. In connexion with the relation of calcium to coagulability, the usual chemical analysis by incineration, even if it were practicable to obtain large quantities of blood, would be of no value. For Sabbatini has shown that the calcium of the blood exists in two forms, a non-dissociable form in combination with protein molecules and a dissociable form. It is only the ionic calcium which has anything to do with coagulation. When oxalic acid is added to blood it is the ionic calcium which is precipitated; the non-dissociable calcium remains unaffected and may be obtained by incineration. But just as it is incapable of reacting with the oxalic acid, so it is incapable of playing the part of ionic calcium in the coagulation process. Blair Bell's method, therefore, does not give the total quantity of calcium in the blood, it is only a measure of the amount of ionic calcium.

As no work done by this method had been published, it was necessary to make sure of its accuracy. It was only after a large amount of practice that I was able to get reliable results. The counting takes a long time. Many of the crystals are not easy to see, and a good deal of experience is required before all of them can be recognized. The following is the way in which I tested the method. Samples of animal serum were obtained from the slaughter-house. The amount of calcium was estimated. Then the same serum was diluted to a known extent, or a known solution in distilled water of calcium chloride was added, and the calcium in the diluted serum was determined. If a serum was found to have an index of 1, where an equal quantity of distilled water was added, it ought to have given an index of 0·5. The difference between the actual amount which was found and the amount which should have been there gave the degree of experimental error. This is really not a fair test, for, as was pointed out to me, to be accurate it would be necessary to weigh the serum and distilled water. Distilled water and serum being of different densities, equal quantities by volume do not quite give a half dilution of the calcium salts in the serum. The following are two examples of the experiments:—

I. 1. Undiluted serum.
The calcium index = 2·270.

2. The same serum + an equal quantity of 1 in 6000 calcium oxide solution.
The calcium index = 1·676.
The index 1·676 should have been 1·635.
Therefore the error = 0·041.

II. 1. Undiluted serum.
The calcium index = 2·287.

2. The same serum + an equal quantity of distilled water.
The calcium index = 1·162.
The index 1·162 should have been 1·143 (2·287 ÷ 2).
Therefore the error = 0·019.

Eight tests were made. Errors of 0·041, 0·019, 0·354, 0·031, 0·181, 0·033, 0·505, and 0·002 were found. It will be seen that they are all very small with the exception of two, 0·354 and 0·505. In the first case the light was poor so that counting was difficult, and in the second case the serum used was a mixture of serums which had been kept for over 48 and 72 hours respectively. In the other cases the serums used were less than 24 hours old. If these two experiments be excluded, there is an average error of 0·053. If they are included it is 0·147. The average amount of calcium in the serum was 2·18, so an error of 0·053 is equal to an error of 2·4 per cent., and an error of 0·147 is equal to an error of 6·7 per cent. In actual practice with blood the error may be a little higher because the débris of the blood corpuscles tend to make the counting rather more difficult. The method, then, is quite sufficiently accurate for comparative purposes, for

the variations in the index which occur after calcium and citric acid are so large as entirely to overshadow the experimental error. To eliminate large experimental errors I made two counts on separate Thoma-Zeiss plates, and discarded the experiment if there was a difference of more than about 0·15. This, however, was seldom necessary.

## The Effect of Calcium and Citric Acid on the Calcium Content of the Blood.

Lime salts are known to be absorbed from the stomach and intestines with difficulty, and the first point to be investigated was whether they had any appreciable effect on the quantity as estimated in the blood. Dr. J. S. Fowler has permitted me to show the charts on p. 157 of the calcium index of two children under his care at the Edinburgh Royal Hospital for Sick Children. The estimations were made at the same time each day, so as to avoid variations due to absorption of calcium from food. In the first chart especially there was a very rapid rise in the index, which was subsequently found to be due to calcium having been given two hours before the blood was taken.

A number of similar observations on healthy people and on hospital patients gave the same result, though once or twice no increase was found, but this was very probably due to some fault in technique.

Citric acid was found to cause a diminution in the amount of ionizable calcium.

W. R. A.
At 11 a.m. the calcium index = 0·92.
At 11.10 a.m. 60 grains of citric acid were taken.
At 12.45 p.m. the calcium index = 0·67.

Citric acid does not of course make any difference to the total quantity of calcium, but it diminishes the amount of the ionizable calcium and increases the amount of the non-dissociable form. C. J. Martin, quoted by Coleman, has found that calcium citrate is formed in the blood, and that this becomes a more complex body with the following formula, from which the calcium ion is not dissociable:—

$$\left\{C_3H_4(OH)\begin{matrix}COONa\\COO\\COO\end{matrix}\!\!>\!Ca\right\}11$$

It may, therefore, be accepted that calcium induces an increase in the quantity of ionizable calcium in the blood and that citric acid diminishes it.

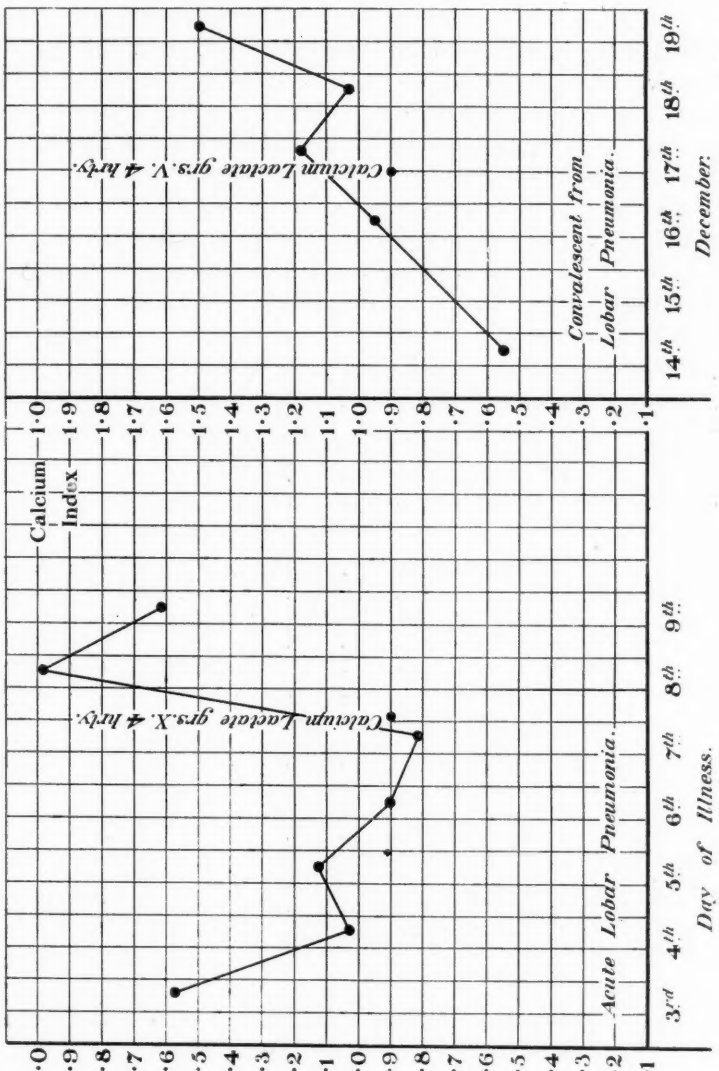


CHART 2.




CHART 3.

### Results showing that Alterations in the Calcium Content of the Blood have no Effect on the Coagulation Time.

Without going further there was already a strong presumption that the amount of variation in the calcium content which can be produced in the body is not sufficient to affect the coagulation time. The calcium index was very variable, depending no doubt on the food which was taken, for the index was found to fall with abstention from food. On the other hand, food had no effect on the coagulation time, which was always constant within the limits of experimental error. The following are examples of experiments to show that though the calcium index was changed the coagulation time remained unaffected. Slight changes occur in the coagulation times, but these are due to experimental error.

T. A.

At 10.10 a.m. the coagulation time . . . . . = 7 min. 15 sec.
At 10.30 a.m. the calcium index . . . . . = 0·93
At 11.30 a.m. 40 grains of calcium lactate were taken.
At 11.37 a.m. the coagulation time . . . . . = 7 min. 45 sec.
At 11.48 a.m. the calcium index . . . . . = 1·28

F. C. A.

At 10.50 a.m. the coagulation time . . . . . = 7 min. 20 sec.
At 11.52 a.m. the calcium index . . . . . = 0·91
At 11.55 a.m. 40 grains of calcium lactate were taken.
At 12.50 p.m. the calcium index . . . . . = 1·14
At 1.1 p.m. the coagulation time . . . . . = 7 min. 10 sec.
At 3.39 p.m. the coagulation time . . . . . = 7 min. 10 sec.

W. R. A.

At 11.6 a.m. the coagulation time . . . . . = 7 min. 45 sec.
At 11 a.m. the calcium index . . . . . = 0·92
At 11.10 a.m. 60 grains of citric acid were taken.
At 12.45 p.m. the calcium index . . . . . = 0.67
At 1.14 p.m. the coagulation time . . . . . = 6 min. 10 sec.
At 3.50 p.m. the coagulation time . . . . . = 7 min.
At 6.35 p.m. the coagulation time . . . . . = 6 min. 35 sec.

Other observations gave similar results.

### The Effect of the Administration of Calcium and Citric Acid on the Coagulation Time and Calcium Content of the Blood.

In the following cases the effect of calcium on the calcium content was assumed to have taken place, and only the effect on the coagulation time was noted.

Calcium Lactate, Gr. 120.

P. M.

| | min. | sec. |
|---|---|---|
| At 11.12 a.m. the coagulation time . . . . . = | 6 | 45 |
| At 11.15 a.m. 120 grains of calcium lactate were taken. | | |
| At 12.8 p.m. the coagulation time . . . . . = | 7 | 30 |

CALCIUM LACTATE, GR. 60.

| F. B. | min. | sec. |
|---|---|---|
| At 5.24 p.m. the coagulation time . . . . . = | 7 | 25 |
| At 5.40 p.m. 60 grains of calcium lactate were taken. | | |
| At 6.26 p.m. the coagulation time . . . . . = | 7 | 25 |
| **T. A.** | | |
| At 9.20 a.m. the coagulation time . . . . . = | 7 | 5 |
| At 9.30 a.m. 60 grains of calcium lactate were taken. | | |
| At 10.50 a.m. the coagulation time . . . . . = | 7 | 30 |
| **M. M.** | | |
| At 10.42 a.m. the coagulation time . . . . . = | 8 | 0 |
| At 11 a.m. 60 grains of calcium lactate were taken. | | |
| At 12.24 p.m. the coagulation time . . . . . = | 9 | 0 |
| **T. A.** | | |
| At 10.15 a.m. the coagulation time . . . . . = | 7 | 0 |
| At 11 a.m. 60 grains of calcium lactate were taken. | | |
| At 12 noon the coagulation time . . . . . = | 8 | 20 |
| At 1.59 p.m. the coagulation time . . . . . = | 8 | 20 |
| **T. A.** | | |
| At 7.47 a.m. the coagulation time . . . . . = | 6 | 40 |
| At 8.18 a.m. the coagulation time . . . . . = | 7 | 50 |
| At 8.52 a.m. the coagulation time . . . . . = | 7 | 55 |
| At 10.37 a.m. the coagulation time . . . . . = | 8 | 23 |
| At 10.45 a.m. 60 grains of calcium lactate were taken. | | |
| At 11.59 a.m. the coagulation time . . . . . = | 7 | 35 |
| At 1.15 p.m. the coagulation time . . . . . = | 6 | 45 |
| At 2.10 p.m. the coagulation time . . . . . = | 8 | 30 |
| **G. G.** | | |
| At 10.34 p.m. the coagulation time . . . . . = | 8 | 53 |
| At 10.40 p.m. 60 grains of calcium lactate were taken. | | |
| At 11.32 p.m. the coagulation time . . . . . = | 10 | 30 |
| At 11.50 p.m. the coagulation time . . . . . = | 8 | 15 |
| **E. R.** | | |
| At 4.48 p.m. the coagulation time . . . . . = | 8 | 20 |
| At 5.13 p.m. 60 grains of calcium lactate were taken. | | |
| At 5.54 p.m. the coagulation time . . . . . = | 9 | 30 |
| **T. A.** | | |
| At 8.49 a.m. the coagulation time . . . . . = | 6 | 40 |
| At 9.35 a.m. 60 grains of calcium lactate were taken. | | |
| At 5.1 p.m. the coagulation time . . . . . = | 7 | 25 |
| **A. G.** | | |
| At 4.30 p.m. the coagulation time . . . . . = | 8 | 0 |
| At 4.35 p.m. 60 grains of calcium lactate were taken. | | |
| At 5.58 p.m. the coagulation time . . . . . = | 6 | 50 |
| **T. A.** | | |
| At 1.59 p.m. the coagulation time . . . . . = | 7 | 20 |
| At 3.15 p.m. 65 grains of calcium lactate were taken. | | |
| At 3.38 p.m. the coagulation time . . . . . = | 8 | 0 |
| At 4.3 p.m. the coagulation time . . . . . = | 7 | 45 |

| | | min. | sec. |
|---|---|---|---|
| At 5.26 p.m. the coagulation time | = | 7 | 25 |
| At 6.53 p.m. the coagulation time | = | 6 | 0 |
| At 8.24 p.m. the coagulation time | = | 6 | 0 |

CALCIUM LACTATE, GR. 40.

F. C. A.

| | | | |
|---|---|---|---|
| At 11.8 a.m. the coagulation time | = | 8 | 55 |
| At 11.10 a.m. 40 grains of calcium lactate were taken. | | | |
| At 11.57 a.m. the coagulation time | = | 8 | 23 |
| At 1.52 p.m. the coagulation time | = | 7 | 55 |
| At 4.18 p.m. the coagulation time | = | 7 | 35 |

T. A.

| | | | |
|---|---|---|---|
| At 5.42 p.m. the coagulation time | = | 9 | 0 |
| At 6.40 p.m. the coagulation time | = | 9 | 13 |
| At 8.30 p.m. 40 grains of calcium lactate were taken. | | | |
| At 10 p.m. the coagulation time | = | 10 | 30 |

F. C. A.

| | | | |
|---|---|---|---|
| At 5.59 p.m. the coagulation time | = | 9 | 0 |
| At 6.56 p.m. the coagulation time | = | 10 | 30 |
| At 8.30 p.m. 40 grains of calcium lactate were taken. | | | |
| At 10.32 p.m. the coagulation time | = | 10 | 0 |

CALCIUM LACTATE, GR. 30.

L. F.

| | | | |
|---|---|---|---|
| At 10.7 p.m. the coagulation time | = | 9 | 3 |
| At 10.10 p.m. 30 grains of calcium lactate were taken. | | | |
| At 10.56 p.m. the coagulation time | = | 8 | 45 |

CALCIUM LACTATE, GR. 20.

T. A.

| | | | |
|---|---|---|---|
| At 10.47 a.m. the coagulation time | = | 7 | 50 |
| At 11.39 a.m. the coagulation time | = | 7 | 40 |
| At 12 noon 20 grains of calcium lactate were taken. | | | |
| At 12.3 p.m. the coagulation time | = | 7 | 55 |
| At 12.47 p.m. the coagulation time | = | 6 | 30 |
| At 1.8 p.m. the coagulation time | = | 8 | 0 |

CALCIUM LACTATE, GR. 15.

J. C.

| | | | |
|---|---|---|---|
| At 7.15 p.m. the coagulation time | = | 8 | 50 |
| At 7.20 p.m. 15 grains of calcium lactate were taken. | | | |
| At 8.44 p.m. the coagulation time | = | 9 | 25 |

CALCIUM LACTATE, GR. 7½.

D. C.

| | | | |
|---|---|---|---|
| At 7.58 p.m. the coagulation time | = | 6 | 0 |
| At 8 p.m. 7½ grains of calcium lactate were taken. | | | |
| At 8.54 p.m. the coagulation time | = | 8 | 20 |

J. C.

| | | | |
|---|---|---|---|
| At 8.13 p.m. the coagulation time | = | 7 | 30 |
| At 8.15 p.m. 7½ grains of calcium lactate were taken. | | | |
| At 10.7 p.m. the coagulation time | = | 8 | 20 |

RESULTS SHOWING THAT THE ADMINISTRATION OF CITRIC ACID HAS NO EFFECT ON THE COAGULATION TIME.

*Conducted under the same conditions as with calcium.*

CITRIC ACID, GR. 120.

P. M. min. sec.

At 4.10 p.m. the coagulation time . . . . . = 7 10
At 4.15 p.m. 120 grains of citric acid were taken.
At 5.34 p.m. the coagulation time . . . . . = 7 15

CITRIC ACID, GR. 60.

D. W. P.

At 11.3 a.m. the coagulation time . . . . . = 8 45
At 11.5 a.m. 60 grains of citric acid were taken.
At 12.9 a.m. the coagulation time . . . . . = 9 15

C. L.

At 8.20 a.m. the coagulation time . . . . . = 7 30
At 8.25 a.m. 60 grains of citric acid were taken.
At 9.6 a.m. the coagulation time . . . . . = 7 20

F. B.

At 8.43 a.m. the coagulation time . . . . . = 7 0
At 8.45 a.m. 60 grains of citric acid were taken.
At 9.33 a.m. the coagulation time . . . . . = 6 50

M. I.

At 9.51 a.m. the coagulation time . . . . . = 7 30
At 9.52 a.m. 60 grains of citric acid were taken.
At 12.31 p.m. the coagulation time . . . . . = 7 45

R.

At 2.53 p.m. the coagulation time . . . . . = 7 0
At 3 p.m. 60 grains of citric acid were taken.
At 3.49 p.m. the coagulation time . . . . . = 6 50

T. A.

At 9.8 a.m. the coagulation time . . . . . = 8 30
At 9.15 a.m. 60 grains of citric acid were taken.
At 10.46 a.m. the coagulation time . . . . . = 8 30

E. W.

At 10.57 a.m. the coagulation time . . . . . = 9 35
At 11 a.m. 60 grains of citric acid were taken.
At 11.56 a.m. the coagulation time . . . . . = 7 30

P. G.

At 11.32 a.m. the coagulation time . . . . . = 8 50
At 11.35 a.m. 120 grains of citric acid were taken.
At 12.25 p.m. the coagulation time . . . . . = 9 20

| | | min. | sec. |
|---|---|---|---|
| P. C. | | | |
| At 7.35 p.m. the coagulation time . . . . . | = | 8 | 25 |
| At 7.40 p.m. 60 grains of citric acid were taken. | | | |
| At 9.41 p.m. the coagulation time . . . . . | = | 9 | 30 |
| D. C. | | | |
| At 6.52 p.m. the coagulation time . . . . . | = | 8 | 0 |
| At 7.4 p.m. the coagulation time . . . . . | = | 9 | 0 |
| At 7.12 p.m. 60 grains of citric acid were taken. | | | |
| At 8 p.m. the coagulation time . . . . . | = | 8 | 0 |
| E. R. | | | |
| At 10.8 a.m. the coagulation time . . . . . | = | 7 | 30 |
| At 10.10 a.m. 60 grains of citric acid were taken. | | | |
| At 1.13 p.m. the coagulation time . . . . . | = | 8 | 55 |

The variations in the time after calcium and citric acid are sometimes in the direction of increase and sometimes of decrease of the time. They are due solely to experimental errors, the commonest being slight differences in the size and shape of the drop of blood. The average coagulation time before calcium was 7 min. 59 sec., and the average after was 8 min. 3 sec. Before citric acid the average was 7 min. 55 sec., and the average after was 8 min. 5 sec. In confirmation of these results a considerable number of estimations with Wright's, Brodie and Russell's, and with a modification of McGowan's method before and after calcium chloride and calcium lactate, failed to show that they had any effect whatever on the time.

### The Amount of Change in the Calcium Content necessary to Produce an Appreciable Effect on the Coagulation Time of Blood *in Vitro*.

Calcium and citric acid, of course, are both capable of altering the coagulability of the blood, but the amount of variation in the calcium content which can be produced by their administration by the mouth is too small to produce any appreciable effect on the coagulation time. Blair Bell has shown that an average of 1 crystal per square, i.e. an index of 1, is nearly equal to a solution of 1 in 3,000 $CaCl_2$, although, as he points out, a comparison between blood and an aqueous solution of $CaCl_2$ is not strictly accurate. He puts the average index at 0·8*. This is equal to a 0·021 per cent. solution of $CaCl_2$, which may be taken as about the average amount of calcium in the blood if it is estimated in terms of the chloride. The extreme limits of variation which I have found have been from 0·008 per cent. to 0·049 per cent. Wright has himself studied this question on oxalated blood. Graduated additions of $CaCl_2$ were made to 5 c.c. or 10 c.c. of oxalated blood in test-tubes, and the coagulation was considered complete when the tubes could be inverted without spilling their contents.

* Private communication.

The following are his results:—

| *Amount of calcium chloride added.* | *Result.* |
|---|---|
| 0·018 % | Fails to clot. |
| 0·036 % | Clots in 1½ min. |
| 0·055 % | Clots in 1 min. |
| 0·110 % | Clots in 2½ min. |
| 0·165 % | Clots in 5 min. |
| 0·183 % | Clots in 6½ min. |
| 0·366 % | Clots in over 60 min. |
| 0·550 % | Fails to clot in 24 hours. |

The three groups are not comparable, as the temperature was sometimes the room temperature and sometimes 37° C., but the times of each group are comparable with each other. It is remarkable that there was no coagulation in the first tube, to which not much less than the normal amount of calcium for human blood was added. The sort of blood used is not stated. The amount of calcium in the second group, with the possible exception of the first tube, is probably more than can possibly be present in the blood *in vivo*, and the same applies still more strongly to the third group.

R. M. Horne found that a considerably greater quantity of calcium than is given by Wright was necessary to delay coagulation. He used ox's blood, receiving 190 c.c. directly into a flask from the animal and then adding 10 c.c. of calcium chloride solutions of different strengths. He found that 0·5 per cent. of $CaCl_2$ delayed coagulation, 1 per cent. delayed it still more, and between 2 per cent. and 3 per cent. was necessary to prevent it. To these figures, of course, it is necessary to add the amount of calcium already present in the blood. The amount was not known. If then 0·1 per cent. (Wright) or 0·5 per cent. (Horne) are required to produce a distinct prolongation of the coagulation time, it is easy to understand that variations between 0·008 and 0·049 may have no effect at all.

## General Conclusions.

1. The coagulation time of the blood is unaffected by the administration by the mouth of soluble calcium salts or of citric acid.

2. The amount of ionizable calcium in the blood is increased by the administration of soluble calcium salts by the mouth, and is diminished by the administration of citric acid, but the increase or decrease which is thus brought about is considerably less than the degree of variation in the calcium content which is necessary before any appreciable effect is produced on the coagulation time.

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# CONGENITAL FAMILY CHOLAEMIA

By HERBERT P. HAWKINS and LEONARD S. DUDGEON

It is certain (1) that a child may be born jaundiced or may become jaundiced soon after birth; (2) that the jaundice may persist with little or no variation for many years, at any rate till middle life; (3) that the spleen in these cases is always enlarged; (4) that there is considerable anaemia with a low colour-index, poikilocytosis, and the presence of nucleated red cells; (5) that nevertheless the patient has good or fair health, can stand intercurrent diseases, and if a woman is able to bear children; (6) that bile-pigment is present in the stools as in health, that it is not present in the urine, but that any darkening of the urine that may be present is due to excess of urobilin; (7) that nevertheless bile-pigment is present in the serum; (8) that this condition tends to appear in more than one member of a family, and in successive generations. 'Congenital family cholaemia or acholuric jaundice' is a term which covers the whole matter.

Little is known of this condition, but the following additional points may be accepted as probably true. Both sexes are equally affected. It is clear that in some cases the jaundice is actually present at birth, but perhaps in some cases little attention is paid to it until it becomes more striking after a year or two. These patients are well grown and not stunted in body or mind, and they may have no feeling or appearance of ill-health. Considering the state of the blood, the maintenance of such good health is astonishing. One of our cases is a policeman on active duty. The ending of these cases and the duration of life are unknown. It is possible that life is not materially shortened. The policeman has reached the age of 27. The fingers are not clubbed. The stools are never acholic. The colour of the skin and conjunctivae is as yellow as in a catarrhal jaundice: it is a real lemon-yellow and not a mere sallowness or muddiness of complexion. Even after many years there is no pigmentation. There seems to be no itching of skin. Though the yellow colour never entirely disappears it may undergo variation. Some of these cases are liable to attacks during which the colour deepens, pain may be experienced over the spleen or the liver or both, and even slight pyrexia may occur. The appetite is good, the bowels act regularly, and there is no evidence of any gastro-intestinal disorder. In none of our cases, and in no similar case which is on record, is there anything to indicate a syphilitic taint in patient or parents, and there is never a suspicion of alcoholic excess. The spleen in this cholaemia is always enlarged, its lower

[Q. J. M., Jan., 1909.]

end reaching to the level of the umbilicus, but this is generally the outside limit. As a rule it is free from tenderness, and the enlargement is discovered accidentally. The liver also may be enlarged, but this is not common, and relatively the enlargement is of less degree. As regards any cirrhotic change in the liver, if it ever supervenes, it must be a very late event, and little is known of the ending of these cases. In a man suffering from this cholaemia who died from influenza-pneumonia Minkowski found no cirrhosis. In Claude Wilson's fatal case (see later), if it may be quoted as an instance of this condition, the liver was considerably enlarged, but it was fatty and not cirrhotic. Case I of our series has reached the age of 27 without sign or suspicion of cirrhosis. On the other hand, in Case IV the liver is enlarged and perhaps unduly firm, though there are no symptoms of cirrhosis. Moreover, enlarged abdominal veins, ascites, oedema of shins, and haematemesis have never been noted in any recorded case.

The state of the blood is important as possibly throwing light on the nature of the condition and on its relation to other diseases. The results of examinations, in these four patients, which in their main features are almost identical, may be thus summarized: Red cells vary from 2,590,000 to 3,676,000, the average being 3,090,000, rouleaux-formation is poor or absent, microcytes are numerous, polychromatophilia is marked, poikilocytosis is well marked; granular degeneration was well marked in one case. In these four cases respectively, 1 megaloblast, 7 normoblasts and 27 megaloblasts, 15 normoblasts and 10 megaloblasts, 5 normoblasts and 1 megaloblast, were seen in counting 500 leucocytes. In two cases "ghosts" were very numerous. The haemoglobin varies from 35 to 70 per cent., the average being 44 per cent.; the colour-index varies from 0·58 to 0·9, the average being 0·69. Fibrin-formation was absent in one case, slight in another; blood platelets were very numerous in one case, scanty in another. The leucocytes vary from 3,800 to 6,120, the average being 4,880, with no real alteration in relative proportions, though there was slight excess of polynuclear neutrophils in one case (adult) and slight lymphocytosis in another case (aged 7). In three cases the serum was strongly tinged with demonstrable bile-pigment. The condition may be summed up as anaemia with low haemoglobin-value, with defective formation (especially microcythaemia), with evidence of regeneration, and with leucopenia.

Records of this cholaemia are scarce, and, though these four cases that we record do not add much to our stock of knowledge, it is possible that they may serve their turn later in some collective investigation.

*Case I.* D. R., aged 27, policeman, was sent to St. Thomas's Hospital in February, 1907, by Dr. S. F. Wright of Lee. He was born in Inverness of Scottish parents, both of whom are alive and well. Four brothers and three sisters are healthy, and none of them have had jaundice or shown any yellowness of skin.

He was sent up on account of 'chronic jaundice'. His own statement was to the effect that he had had jaundice ever since he could remember. His mother stated by letter that he was jaundiced at or about birth, and had

remained so ever since, without variation. She added that the pregnancy and delivery were normal, 'though the fluid was scanty.' It may be said at once, that with the exception of one illness he had always enjoyed good health in spite of the jaundice, and this is shown by the fact that he had been admitted into and had served six years in the police force. In fact he sought advice now only in the hope of improving his colour and so avoiding the remarks addressed to him on this account. His one previous illness occurred five years ago, when he had a recurring pleural effusion necessitating paracentesis on four occasions. The fact that he was then (as always) jaundiced led the doctor under whose care he was to take a grave view, suspecting new growth or hydatid. However, he made a perfect recovery. The condition of the spleen at that time cannot be ascertained.

He had always been temperate, had never had any venereal disease, and had not been out of this country.

On examination he was found to be well built and strong, weighing 159 lb. stripped. His lemon-yellow colour was about the degree which is seen in the height of a common catarrhal jaundice, skin and conjunctivae being equally affected. He had never suffered from itching of the skin. His eyes were rather prominent, but Stellwag's and von Gräfe's signs were not present, and there was no enlargement of the thyroid. There was no sign of disease in the chest, except some evidence of a thickened pleura on the right side. The spleen was considerably enlarged, extending down to the level of the umbilicus. It was hard and sharp-edged but not tender. The liver was not enlarged. There was no sign of disease of the nervous system. The temperature was normal, the pulse 78, and the tongue clean and steady.

He showed an extraordinary development of glistening pearly-white cutaneous atrophic lines, which could be felt with the finger as troughs, many of them being three-sixteenths of an inch in breadth. They were oddly arranged. One group radiated from the umbilicus to the groin and flank on the right side only, the skin on the left side being normal. Another patch occupied the back of the right thorax, and a few were placed symmetrically with these on the left side. Of the right thigh the anterior and outer surfaces were covered with them, and there were a few on the inner surface of both thighs. They were thus chiefly right-sided, and it is noteworthy that his pleurisy was also on the right side. The patient did not know when they had appeared, but from the fact that he paid no attention to them it may be concluded that they were of long standing. It may be taken as certain that there had never been any stretching of the skin at the site of the atrophic lines, and a tropho-neurotic origin seems to afford the only explanation.

Here, then, was a man in perfect health, in active work as a policeman, who for twenty-seven years had been as yellow as one suffering from catarrhal jaundice. But the stools were of normal colour and consistence, and the bowels acted regularly, and it may be said that as regards both their biliary contents and their general functions the intestines were healthy. The urine was rather high-coloured, but the colour would not have suggested the presence of bile and in fact no bile was present. Its amount was normal, averaging 45 oz. a day. The specific gravity was 1020, acid with a deposit of amorphous urates and traces of carbonates. Bile-pigment and bile-acids were absent. Urobilin was present and easily demonstrated. There was no albumen, globulin, or nucleo-proteid; no sugar or any reducing substance. Cammidge's tests, A and B, were negative. No acetone, acetoacetic acid, or indican could be found. The urea was 15 gr. to the oz.

So that though he had the appearance of jaundice, the bile-contents of the intestine were normal, and the high colour of the urine was due to urobilin and not to bile-pigment. But his blood-serum contained bile-pigment. The following is an account of his blood:—

'Rouleaux-formation poor, very slight fibrin-formation, platelets very numerous, poikilocytosis present, serum strongly tinged with bile-pigment.

'Red cells 3,676,000, haemoglobin 70 per cent., index 0·9, leucocytes 6,120. Differential count:—

| | |
|---|---|
| Polynuclear neutrophils | 411 = 82·2 % |
| Polynuclear eosinophils | 3 = 0·6 % |
| Small lymphocytes | 6 = 1·2 % |
| Large lymphocytes | 23 = 4·6 % |
| Large hyaline cells | 49 = 9·8 % |
| Transitional cells | 3 = 0·6 % |
| Coarsely granular basophilic | 3 = 0·6 % |
| Finely granular basophilic | 2 = 0·4 % |

'One megaloblast seen. Granular degeneration present.'

In September, 1908, he was still in perfect health, and had never been off duty for sickness in the past twenty months. There was no change to record in colour or appearance. He did not seem to have had any attacks in which the yellow colour deepened, and he had had no pain.

*Case II.* G. P., a girl aged 11, was brought to one of us in September, 1907, by Dr. Arnott of Brixton Road. She was well grown and well nourished, weighing 66 lb., with fair hair, looking in perfect health but jaundiced. The skin and conjunctivae were lemon-yellow as in the preceding case, and with her fair hair and regular features the effect was becoming. Her mother stated that the child became yellow about the second week after birth, and that she had been yellow ever since. But at the age of 7 she became for a time more yellow and was ill for some weeks, as if an acute attack was superposed upon the chronic condition, and at this time her doctor noticed that both liver and spleen were enlarged. With the exception of measles she had had no other illness, and, though recently she had had some discomfort in the epigastrium after meals, it is clear that she had enjoyed very good health. There was no evidence of any heritable disease in the family, the father and mother were healthy, and there was no evidence of jaundice in previous generations.

On examination it was found that the spleen was greatly enlarged, extending one inch below the umbilicus. It was hard but not tender, and the child had had no pain in this region. The liver was slightly enlarged, the edge extending one inch below the costal margin in the right nipple-line, but it did not seem to be indurated. Her stools were said to be of normal colour. As in the preceding case the blood-serum contained bile-pigment, but in this case not only was bilirubin absent from the urine but there was no excess of urobilin. In fact the urine was of normal colour and showed no abnormality. The blood, however, showed a higher grade of anaemia than in the case of the policeman:—

'Red cells 3,043,000, haemoglobin 35 per cent., index 0·58, leucocytes 3,800. Serum strongly tinged with bile-pigment. "Ghosts" numerous, poikilocytosis well marked. Some polychromatophilia. Macrocytes and microcytes very numerous. No nucleated red cells seen.

'Differential count:—

| | |
|---|---|
| Polynuclear neutrophils | 256 = 64·0 % |
| Polynuclear eosinophils | 3 = 0·75 % |
| Small lymphocytes | 93 = 23·25 % |
| Large lymphocytes | 26 = 6·5 % |
| Large hyaline cells | 15 = 3·75 % |
| Transitional cells | 1 = 0·25 % |
| Coarsely granular basophilic cells | 6 = 1·5 %' |

As has been mentioned, she seems to have had some temporary increase of the jaundice at the age of 7. Apart from this there is no history of painful attacks. On one occasion after a fright it was thought that the colour deepened.

She was started upon a long course of arsenic. In March, 1908, i.e. after six months, her general health remained as before. She had gained 1½ lb. in weight. There was slight improvement as regards haemoglobin percentage, which was now 55 per cent. with an index of 0·9. In most respects the blood remained as before; the red cells were 3,028,000, poikilocytosis was very marked, and bile-pigment was present in the serum, but 15 normoblasts and 10 megaloblasts were seen in counting 500 leucocytes, whereas no nucleated red cells were seen before. The leucocytes had risen to 8,600. She had developed a haemic systolic murmur at base and apex of heart.

In September, 1908, six months later, she remained in good health, going to school and never being ill. Her colour and spleen were unchanged. The urine contained no bile-pigment or excess of urobilin. She had gained 4 lb. in weight. She had taken arsenic nearly continuously for ten months, but in spite of this the blood showed some fall in value. The red cells were 2,912,000, rouleaux-formation was fair, poikilocytosis was marked, microcytes were especially numerous, leucocytes were 3,000 per c.mm., 13 normoblasts were seen in counting 500 leucocytes. The haemoglobin was 45 per cent., index 0·7. Bile-pigment was present in the serum.

This patient had two sisters. One, aged 15, showed no sign of disease. The other, aged 13, was in the same state as her younger sister, and, as will be seen from the subjoined account, the condition is identical.

*Case III.* J. P., aged 13, sister of the preceding case, was described by her mother as having often been yellow from her birth. On two occasions she had jaundice, and her doctor then noted that the spleen was enlarged. On examination she had distinct icteric tinge of skin and conjunctivae, not so marked as in her sister, but quite enough to attract attention and to deserve the term jaundice. Her parents, however, had apparently become so accustomed to her colour that they hardly considered it to be abnormal. It is clear that, like her sister, she had been yellow from birth, perhaps with variation in the depth of the colour, and that the two attacks of jaundice described were really aggravations of an existing state.

Like her sister, this child had always had good health. When she was seen she appeared to be perfectly well, strongly-built and well-nourished. The spleen extended down to the level of the umbilicus, but the liver was not enlarged. The stools and the urine were said to be always of normal colour. As in the case of her sister, one was surprised to find so high a degree of anaemia considering the good health and strength. Blood-examination showed—

'Red cells 3,038,750, haemoglobin 35 per cent., index 0·58, leucocytes 4,160. Serum strongly tinged with bile-pigment. "Ghosts" very numerous, poikilocytosis marked, some polychromatophilia, macrocytes and microcytes very numerous, no nucleated red cells seen.

'Differential count:—

| | |
|---|---|
| Polynuclear neutrophils | 230 = 57·5 % |
| Polynuclear eosinophils | 6 = 1·5 % |
| Small lymphocytes | 93 = 23·25 % |
| Large lymphocytes | 44 = 11·0 % |
| Large hyaline cells | 25 = 6·25 % |
| Coarsely granular basophilic cells | 2 = 0·5 %' |

She was placed on a course of arsenic. At the end of six months she remained in the same good health as before. The changes in the blood after six months of arsenic were precisely the same as in her sister under the same conditions. Haemoglobin had increased to 58 per cent., and this increase with a slight fall in the number of red cells gave an index of 1·0. The leucocytes had risen to 10,120. Bile-pigment was present in the serum as before. Five normo-

blasts and one megaloblast were seen in counting 500 leucocytes, whereas no nucleated red cells were seen on the previous examination. She also had developed haemic murmurs.

In September, 1908, she like her sister remained in good health. She had gained 8 lb. in weight. In all other respects, colour, spleen, and urine, there was no change. She also had taken arsenic for ten months, but the blood showed a slight deterioration as compared with previous examinations: 'Red cells 2,609,375, poikilocytosis, microcytes very numerous, rouleaux-formation bad, haemoglobin 45 per cent., index 0·8, leucocytes 6,560, bile-pigment in serum.'

*Case IV.* T. B., a boy aged 7, was admitted into St. Thomas's Hospital in October, 1907, under Dr. A. E. Russell, who kindly allowed us to make use of the case. There was no history of jaundice or other disease in the family. His mother was examined and found to be healthy, a sister aged 22 was also healthy. This boy was born jaundiced and had remained jaundiced. He was said to be delicate but he had had no actual illness. On admission he had the degree of yellowness of skin and conjunctivae which one associates with a catarrhal jaundice. Though he never fell below this degree of yellowness, he apparently was liable to attacks (as Case III) in which the colour temporarily deepened, and in these attacks there was some pain in the right hypochondriac region. The spleen was enlarged, extending down to the umbilicus, rounded, hard, and free from tenderness. The liver also was enlarged, the edge in the right nipple-line being nearly on a level with the umbilicus: it was smooth, hard, and not tender. The urine contained a trace of albumen, but no bile-pigment and no urobilin. The stools were of normal colour. There was no sign of disease elsewhere and no evidence of congenital syphilis. The blood showed considerable change:—'Red cells 2,593,000, haemoglobin 35 per cent., index 0·7, leucocytes 5,440: rouleaux-formation and fibrin absent, marked poikilocytosis, blood platelets scanty, polychromatophilia and granular change were marked, 7 normoblasts and 27 megaloblasts seen in counting 500 leucocytes: slight relative lymphocytosis.'

He was treated by mercurial inunction and iodipin for six weeks. At the end of this time both liver and spleen seemed to have diminished in size, but the jaundice remained unaltered. Under the use of mercury the red cells dropped to 1,618,000, but on his discharge from Hospital there was some improvement, red cells rising to 3,325,000, but megaloblasts and normoblasts remained as numerous as before, otherwise there was no change.

A year later there was no change to record. The boy was reported to be in fairly good health and growing normally. In the past year he had had some attacks in which the yellowness had deepened with abdominal pain, sometimes associated with sweating and sickness, but he had not required any medical care.

Hayem described five cases under the title 'chronic splenomegalic infectious jaundice'. He seems to consider that this condition is a manifestation of hereditary syphilis, and he has no faith in the theory of a haemolytic origin.

The two cases reported by Thomas Barlow and Batty Shaw under the title 'inheritance of recurrent attacks of jaundice and of abdominal crises with hepato-spleno-megaly' seem to be of the same nature as those we have described. The case of the boy aged 16 reported by them differs only from our cases in that the jaundice was more variable, but perhaps it was not more variable than in Case III of our series. He was pale and waxy at birth, with enlargement of liver and spleen, became permanently jaundiced at the age of 5, and during the next eleven years he was liable to attacks of increased yellowness, with pain in

right or left hypochondrium. Case IV of our series had similar painful attacks. The liver was slightly enlarged, the spleen extended two inches below the umbilicus. The urine was high-coloured and contained abundant urobilin but no bile-pigment. The blood-change was precisely the same as in our cases and nucleated red cells were present, but no mention is made of bile-pigment in the serum. This boy's mother, aged 47, had jaundice at the age of 4, and had had frequent attacks up to date. She seems to have been permanently icteric, the liver and spleen were considerably enlarged, there was moderate anaemia with poikilocytosis, but no excess of urobilin in the urine.

Pollak describes a girl aged 8, whose history and condition are absolutely identical with those of our cases. She had been almost always yellow. The spleen was enlarged. The blood contained 3,200,000 red cells per c.mm. with poikilocytosis and polychromatophilia: the leucocytes were 4,600. The urine showed urobilin but no bile-pigment: the stools were of normal colour. There is no mention of bile-pigment in the serum. Her mother was apparently liable to jaundice for several years, and this woman's mother had jaundice for years before her death. He has seen three other similar cases. Of these, two were sisters, and their mother, her mother, and her grandmother were said to have had lifelong jaundice.

It is possible that Claude Wilson's cases belong to the same class. He reports six cases in three generations, a mother, her daughter and two grandsons, her son and one granddaughter. In five of these patients the spleen was found to be enlarged in the first few years of life, and the enlargement may well have existed at a still earlier date, but in the case of the mother from whom these five were descended the enlarged spleen was not discovered till the age of 33. She lived to the age of 63. In one important respect, however, these six cases differ from the four cases which we describe, in that they do not seem to have been truly jaundiced. It is perhaps only a matter of degree and of words, but our patients have been of a brilliant lemon-yellow colour from first to last, whereas as regards Wilson's cases the terms 'sallow, subicteric, semi-olive' are used, though two of the children always turned 'the colour of a daffodil' after a cold bath. There is no mention of urobilin in the urine or of bile-pigment in the serum.

Under the title 'anaemia with enlargement of the spleen, particularly the family form', Cowan describes two cases which bear a close resemblance to this group. In one case, aged 21, the spleen was found to be enlarged at the age of 9, and his colour was pale and 'yellowish'. At the time of writing he is described as 'evidently anaemic, and both skin and mucous membranes were distinctly yellow'. In the other case, aged 19, the liver was found to be enlarged at the age of 7, and at the time of writing both liver and spleen were enlarged. It is said of him that 'the skin generally was pale and somewhat yellow in tint'. The blood-change had the same characteristics as in our cases, and normoblasts and megaloblasts were present. There is no mention of bile-pigment in the serum. In one of these cases the urine was dark but did not contain urobilin.

Gilbert and Lereboullet describe this 'simple family cholaemia' in accurate terms. They lay stress on its appearance in more than one member of a family and in ancestors and collaterals. They consider that it generally begins or is present at birth. Their observations show that urobilinuria is the rule, though transitory outbursts of choluria may occur, and that bile-pigment is nearly always present in the serum. Our cases and the cases quoted here from other sources are in exact agreement with the account given by these two observers. They go further, however, and propound the theory that there is a complete chain consisting of family cholaemia, transitory or chronic jaundice, splenomegalic jaundice, and hypertrophic biliary cirrhosis, all these conditions belonging to one group. This view may be correct, though it carries us no further towards an explanation, and it is true that biliary cirrhosis, like this simple cholaemia, shows a tendency to familial occurrence. But they go still further and expand the term 'simple cholaemia' to cover a multitude of conditions great and small in a theory which will hardly meet with general acceptance. As being all alike dependent on the presence of bile in the serum, they bring together all manner of dark and muddy complexions, melanodermy, and pigmentary diseases, and couple these with wide secondary conditions including numerous skin-diseases, gastro-intestinal, nervous, renal, articular, and cardiac diseases of various kinds. All this stands in need of confirmation. The experience of the Clinical Laboratory of St. Thomas's Hospital shows no such frequent presence of bile-pigment in the serum. From an examination of a very considerable number of sera obtained from all possible sources it may be said that bile-pigment is present only in the serum of patients obviously jaundiced or in the serum of patients in whom jaundice is just going to appear. It may be mentioned, however, that in pernicious anaemia the serum has often a peculiar coloration somewhat resembling bile-pigment, but failing to give the chemical test for that substance and not giving any definite spectrum of blood-pigment or of its derivatives.

In attempting an explanation of this congenital cholaemia we have one clear fact, that these are cases of jaundice with bile in the blood-serum in greater or less amount, and not cases of splenic anaemia with mere sallowness resulting from cell-poverty.

### Is the Condition due to an Escape of Normal Bile into the Hepatic Lymphatics at the Site of Manufacture?

On this hypothesis it may be simply suggested that there is some congenital defect in the minute anatomy of the liver, so that by some abnormal communication bile enters into the lymphatics as readily as into the biliary canaliculi. Or the equally simple suggestion may be adopted that there is some defective and obstructive development of the larger biliary passages whereby such an increased bile-pressure is produced in the whole or in part of the biliary system as leads to absorption by the hepatic lymphatics. On these theories it must be supposed that the bile in the blood is in sufficient amount to colour the skin, while it is not sufficient to appear in the urine, being converted into urobilin in

the kidneys according to the observations of Gilbert and Herscher, and at the same time it must be supposed that the enlargement of the spleen and the blood-changes are secondary effects of the cholaemia so produced. These simple explanations stand or fall on the possibility that the blood-change is merely due to the continued presence of bile in the blood, and it may be said at once that no such effects are seen to result from long-continued jaundice of common obstructive origin. A moderate loss of red cells and a decrease of haemoglobin occur without other change in such cases. Moreover, in common obstructive jaundice it has been shown (Vaquez, Ribierre, von Limbeck in catarrhal jaundice) that there is an increased resistance of the red cell to saline solution and an increased size of the cell as compared with the healthy state. Now it can be shown that in both these points, i. e. fragility and size, the red cell in this cholaemia is even below the level of the healthy standard.

### Does the Condition depend on Abnormal Destruction of Red Cells, the Cholaemia being a Secondary and Unimportant Result?

The occurrence of jaundice of haemolytic origin, both natural and experimental, is allowed. How in haemolytic jaundice the haemolysis produces cholaemia is not so clear. The explanation commonly received is that the same poison which effects the haemolysis sets up during its excretion a catarrh of the small bile-ducts, whereby a mild obstructive jaundice is produced. It is possible also that the mere excess of blood-pigment which the liver must deal with in such cases has a similar irritant effect, or it may be a matter simply of increased viscidity of the bile which leads to some absorption by the hepatic lymphatics. It is difficult to believe that the jaundice in our cases can be due to any infectious agency, considering the good health and the long life of these patients. This matter, however, of the relation between haemolysis and jaundice is a side-question, and its obscurity need be no bar to accepting the theory that these cases are of haemolytic origin, if any facts point in that direction.

Now apart from the presence of iron in the liver, actual proof of haemolysis, even in pernicious anaemia, is hard to come by during life. It is open to question how far observations *in vitro* may be applied to circulating blood.

The evidence as regards haemolysis in these cases stands thus:—

1. [1] Observations of one of us (L. S. D.) on the haemolytic property of the serum of the two sisters, Case II and Case III:—

(*a*) Serum of Case II on a 5 per cent. suspension of her own red cells: no haemolysis.

(*b*) Serum of Case II on a 5 per cent. suspension of red cells of Case III: no haemolysis.

(*c*) Serum of Case III on a 5 per cent. suspension of her own red cells: no haemolysis.

[1] In these experiments a graduated dilution of the serum was made, as is usually employed in such experiments.

(*d*) Serum of Case III on a 5 per cent. suspension of red cells of Case II : no haemolysis.

Pollak (loc. cit.) obtained similar negative results in his patient.

2. But as regards the structure of the red cells as shown by their resistance to saline solution of various strengths, positive results were obtained :—

*Case II.*

| *Sodium chloride in distilled water.* | *Haemolysis.* |
|---|---|
| 0·1 % | complete. |
| 0·2 % | complete. |
| 0·3 % | complete. |
| 0·4 % | complete. |
| 0·5 % | marked. |
| 0·6 % | slight. |
| 0·7 % | none. |
| 0·8 % | none. |
| 0·9 % | none. |
| 1·0 % | none. |

This may be compared with an identical simultaneous test of the observer's blood :—

| *Sodium chloride in distilled water.* | *Haemolysis.* |
|---|---|
| 0·1 % | complete. |
| 0·2 % | complete. |
| 0·3 % | partial. |
| 0·4 % | none. |
| 0·5 % | none. |
| 0·6 % | none. |
| 0·7 % | none. |
| 0·8 % | none. |
| 0·9 % | none. |
| 1·0 % | none. |

*Case III.*

| *Sodium chloride in distilled water.* | *Haemolysis.* |
|---|---|
| 0·1 % | complete. |
| 0·2 % | complete. |
| 0·3 % | complete. |
| 0·4 % | partial. |
| 0·5 % | slight. |
| 0·6 % | tingeing. |
| 0·7 % | none. |
| 0·8 % | none. |
| 0·9 % | none. |
| 1·0 % | none. |

3. Similar results indicating abnormal fragility of the red cells in these cases of congenital cholaemia have been obtained by Chauffard. He found that haemolysis commenced at 0·7, was distinct at 0·6, and complete at 0·4. Pollak, however (loc. cit.), obtained no such results. Many French observers (Chauffard, Widal, Ribierre, Vaquez) put trust in this saline test as a proof of increased corpuscular fragility, and secondarily take such results as are given above (which they also have obtained) as indicating that haemolysis occurs in the

circulating blood of these cases. Hayem thinks that no such conclusion can be drawn from observations on shed blood, and refuses the term 'haemolytic jaundice' to the cases which he has recorded. He points out that in conditions such as haemoglobinuria, in which haemolysis is most assured, there may be no visible jaundice and there is no bile-pigment in the serum.

4. It is a curious fact, however, that in one case of this congenital cholaemia, Bettmann observed attacks of haemoglobinuria. He found that he could produce this effect by exposure to cold, which is interesting in relation to the children reported by Wilson (loc. cit.) in whom a cold bath produced a 'daffodil colour'.

5. It must be mentioned that Guinon, Rist, and Simon record a case apparently of this nature, a girl aged 10, with chronic variable jaundice, enlarged spleen, urobilinuria, and as a rule oligocythaemia. But with an exacerbation of the jaundice the red cells temporarily rose to 6,000,000–7,600,000 with cyanosis, so that at the moment the case was apparently one of splenomegalic polycythaemia. A somewhat similar case is recorded by Mosse in a man aged 58, who with chronic acholuric jaundice, enlarged spleen, and urobilinuria, had a red-cell count of 6,750,000–7,825,000, and haemoglobin 100–110 per cent.

6. The two sisters who were given a long course of arsenic showed no improvement under its use. Considering the benefit uniformly derived in pernicious anaemia from the use of arsenic, the lack of improvement here would at any rate not suggest a haemolytic origin. The experiments of Gunn tend to show that arsenic has considerable effect in increasing the resistance of red cells to saline solution of various strengths, even so dilute a solution of arsenious acid as 1 in 400,000 producing a perceptible effect.

There is some evidence, therefore, indicating that the red cells are abnormally fragile, while the serum shows no haemolytic property. But certain other points are interesting in the serum and red cells of these cases. In a paper recently contributed to the Proceedings of the Royal Society by one of us (L. S. D.), it has been shown that the washed red cells in certain diseases may be agglutinated by normal serum, and that 'immune serum' may be capable of clumping normal red cells, while no reaction takes place between the immune serum and red cells either from the same case or from similar examples. Saturation-agglutination experiments still further emphasize these facts.

Now in Cases II and III of our series, as is shown below, no auto-agglutination occurred, but when the 'immune serum' from either case was mixed with washed normal red cells marked clumping was noted. Normal serum had no agglutinative property with 'immune red cells'. Saturation experiments gave additional evidence regarding these results. It will thus be seen that the serum of these children must contain some specific property which allows this form of agglutination to take place. It may be remarked that the agglutination which occurs in these cases is not necessarily due to the presence of the bile-pigment, as the best results in this direction are observed apart from the presence of this substance.

From these agglutination experiments it was considered probable that this specific property in the serum would also have the power to sensitize red cells, preferably normal, and thus allow them to be rapidly engulfed in the presence of normal leucocytes. As is shown below, this was not found to be the case, as little phagocytosis was observed, in whatever way the experiments were carried out.

*Agglutination Experiments.*

*Case II.* 1. 1 vol. serum of Case II + 1 vol. of a 5 per cent. suspension of her own washed red blood corpuscles.
No agglutination.

2. 1 vol. serum of Case II + 1 vol. of a 5 per cent. suspension of washed red blood corpuscles of Case III.
No agglutination.

3. 1 vol. serum of Case II + 1 vol. of a 5 per cent. suspension of washed *normal* red blood corpuscles.
Marked agglutination.

4. 1 vol. *normal* serum + 1 vol. of a 5 per cent. suspension of washed red blood corpuscles of Case II.
No agglutination.

*Saturation-Agglutination Experiments.*

1. Serum of Case II saturated with *normal* red blood corpuscles for 18 hours at 37° C.—centrifugalized—the clear fluid then added to *normal* red cells.
No agglutination.

2. Serum of Case II saturated with red cells of Case III for 18 hours at 37° C.—centrifugalized—clear fluid + normal red corpuscles.
Marked agglutination.

*Case III.* 1. 1 vol. serum of Case III + 1 vol. of a 5 per cent. suspension of her own washed red blood corpuscles.
No agglutination.

2. 1 vol. serum of Case III + 1 vol. of a 5 per cent. suspension of washed red blood corpuscles of Case II.
No agglutination.

3. 1 vol. serum of Case III + 1 vol. of a 5 per cent. suspension of washed *normal* red blood corpuscles.
Marked agglutination.

4. 1 vol. *normal* serum + 1 vol. of a 5 per cent. suspension of washed red blood corpuscles of Case III.
No agglutination.

*Saturation-Agglutination Experiments.*

1. Serum of Case III saturated with *normal* red blood corpuscles for 18 hours at 37° C.—centrifugalized—the clear fluid then added to normal red cells.
No agglutination.

2. Serum of Case III saturated with red cells of Case II for 18 hours at 37° C.—centrifugalized—clear fluid + normal red corpuscles.
Marked agglutination.

*Opsonic Experiments.*

1. 1 vol. serum of Case II + 1 vol. of a 5 per cent. suspension of her own red blood corpuscles in normal saline + 1 vol. of washed normal leucocytes.
   50 cells contained one red cell.

2. 1 vol. serum of Case II + 1 vol. of a 5 per cent. suspension of red cells of Case III + 1 vol. of washed normal leucocytes.
   50 cells contained 7 red blood corpuscles.

Similar experiments were made with the serum and red cells obtained from these cases and *normal* serum, but no greater phagocytosis occurred than in the above experiments.

The tubes were incubated for 15 minutes at 37° C.

*Conclusions.*

1. It is probable that the primary change lies in the blood-forming and not in the biliary system.

2. It is probable that this primary change is a 'congenital familial' defect rather than an 'acquired' defect, toxic, metabolic, or infectious.

3. It is possible that this primary change becomes operative and visible through haemolysis.

4. If the secondary phenomena are due to haemolysis, it is probable that the haemolysis should be attributed to defective red cells rather than to any property residing in the serum.

5. The serum, however, seems to possess a specific agglutinative property.

6. It is possible that the compound in which haemoglobin exists in the red cells is below the standard of normal stability from first to last.

7. It seems that, unlike pernicious anaemia and splenic anaemia, this condition shows no improvement under arsenic.

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# NOTES UPON THE CARDIO-RESPIRATORY MURMUR AND ITS RELATIONSHIP TO OTHER PHYSICAL SIGNS[1]

By THOMAS LEWIS

Those who have experience of an out-patient department at a hospital for diseases of the chest can hardly have failed to note the frequency of the occurrence of the physical sign usually known as the cardio-respiratory murmur. Yet an examination of the textbooks, or of those sections of the modern 'systems' dealing especially with chest affections, reveals the unsatisfactory nature of our knowledge both of its occurrence and causation.

The notes, of which the accompanying remarks are but a brief summary, were compiled during the early months of the current year. The paper will be confined, so far as possible, to a statement of results, which may or may not be found of value.

While taking some preliminary notes, it was found that the physical sign under discussion was so frequently met with that it became necessary to limit the examination and charting of it to three patients during any particular afternoon. The procedure adopted was not selective. The first three new patients presenting themselves, and exhibiting the sign, were chosen, and full details of all physical signs in the chest were charted or noted. In this way, observations were made early during the afternoon, and consequently during that portion of the visit when accuracy was most likely to be ensured. On the other hand, the method carried with it a disadvantage, in that the male patients being first in attendance, observations were often confined to them. In all 48 cases were collected and watched for shorter or longer periods, of whom 35 were males and 13 were females.

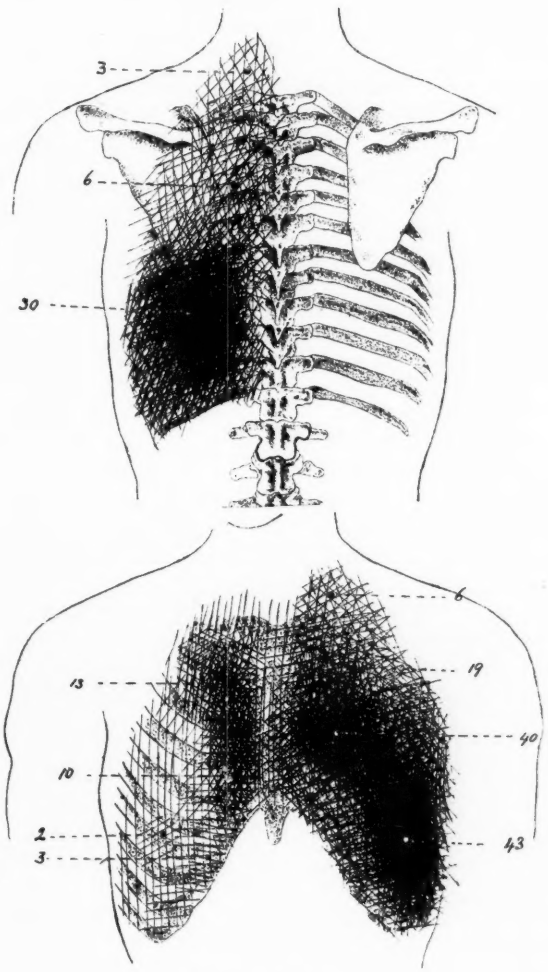
The physical sign considered is a variety of cog-wheel breathing. It consists of interrupted breath sounds; the interruption being regular, and having a rhythm of obvious cardiac origin. The interruptions in a particular respiratory act vary a good deal in rate, but are always directly related to the rate of the heart-beat. It would perhaps be more strictly correct to speak of the breath sounds as continuous, with regular periods of increased intensity; but as the breath sound between the 'cogs' is often difficult to appreciate, this is perhaps an unnecessarily fine distinction. The 'cogs' vary very greatly in intensity, and also in number, during a particular respiratory act, the last

[1] Based upon observations made at the City of London Hospital for Diseases of the Chest.

[Q. J. M., Jan., 1909.]

variation naturally depending upon the rate of the heart-beat and upon the length of the respiratory phase. As a general rule, the cogs are apparent only during deep breathing, but on occasion also with normal breathing. In a very few cases in the series they have been entirely confined to normal breathing.

The distribution of the physical sign over the chest is best appreciated by




FIGS. 1 AND 2.

reference to the accompanying diagrams (Figs. 1 and 2), which are composite pictures of the distribution in the 48 cases. The diagrams have been constructed by shading the affected area of each chest upon the same diagram, by lines approximately equidistant. While the method is not strictly accurate, it is sufficiently so, and eventually gives a fair idea of the frequency of the

occurrence of the sign in any particular locality. It has been rendered numerically accurate by attaching the actual figures to the more important areas.

The diagrams show that in the 48 cases the physical sign occurred—

| | |
|---|---|
| Outside the apex in the fifth and sixth spaces in | 43 |
| In the fourth and fifth spaces along the left border of the heart in | 40 |
| In the region of the angle of the left scapula in | 30 |
| In the first and second left interspaces in | 19 |
| Over the second right costal cartilage in | 13 |
| In the inner end of the fourth right interspace in | 10 |
| At the left apex anteriorly and in the left interscapular region in | 6 |

It will be at once obvious from the diagrams that the frequency of occurrence at any spot is almost entirely controlled by proximity of that spot to the heart.

### Relation to Inspiration and Expiration.

It will be sufficient to state that in the 48 cases it was found in all that the physical sign was entirely dependent upon the respiratory acts and was

Fig. 3.

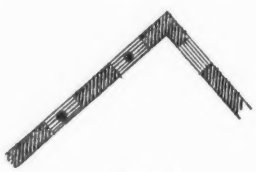


Fig. 4.

never audible when breathing was suspended. In 30 of the cases it was audible in inspiration only, in one in expiration only. In 17 it was heard both in inspiration and expiration; and of these, 6 exhibited it most markedly in inspiration and 3 in expiration.

The observations were, so far as the above-quoted figures are concerned, confined to the point of maximum intensity, as a rule to a point outside the apex beat, occasionally in the third and fourth left spaces or at the angle of the scapula. In a few instances the observations were made at several points, and were then usually in agreement.

Before passing to the inter-relationship of this and other physical signs, several further remarks may be of interest. On several occasions there were, in addition to the cogs timed to occur at or about the onset of ventricular systole, other cogs dispersed between them (Fig. 3). They were definitely presystolic in time, and the suggested auricular origin was confirmed by their appearance in the following situations:—In four cases (Nos. 22, 26, 27, and 36) they were confined to the inner end of the fourth left interspace. In one case they occurred to the right and left of the sternum at the same level (No. 20). In one case they are noted as occurring over the front of the sternum (No. 11).

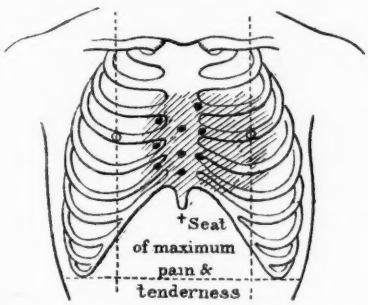



FIG. 5. March 30, 08. The area of cardio-respiratory murmur is charted. There were fine crepitations of the fixed variety over the lower part of the sternum. Some superficial skin tenderness was noted in the epigastrium. These were the only physical signs present.

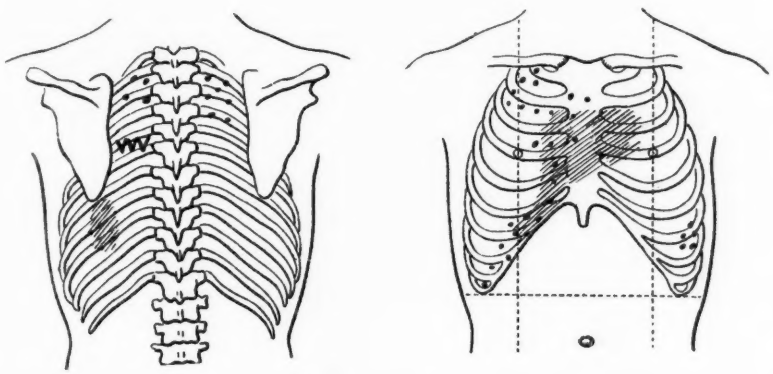


FIG. 6. April 6, 08. Pain and cough gone; said he was better. The râles had spread and the distribution of the murmur had altered; a patch had appeared at the back. There was friction over the lower apex on the left side, and fixed crepitations over both apices.

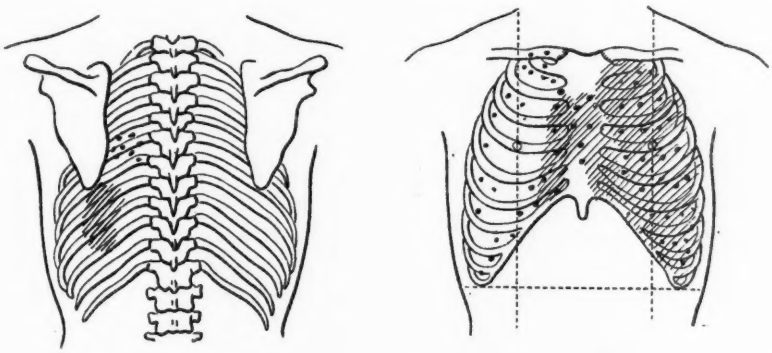


FIG. 7. April 13, 08. The cough had returned. The murmur was over the whole left chest in front and to right of sternum as before. The superficial râles were abundant over the whole front of the chest, and at the left lower apex posteriorly. The friction had gone.

Lastly, in a single case well-marked cogs were heard in the fourth left interspace, each preceded by a single dry and fixed râle (No. 15, Fig. 5). These combined physical signs are diagrammatically represented in Figs. 3 and 4.

In a number of cases the cardio-respiratory murmur has been found to be constant in character and distribution for considerable periods, extending as long as three months. On the other hand, its gradual development and spread, or gradual subsidence, have been observed. An example is illustrated in the

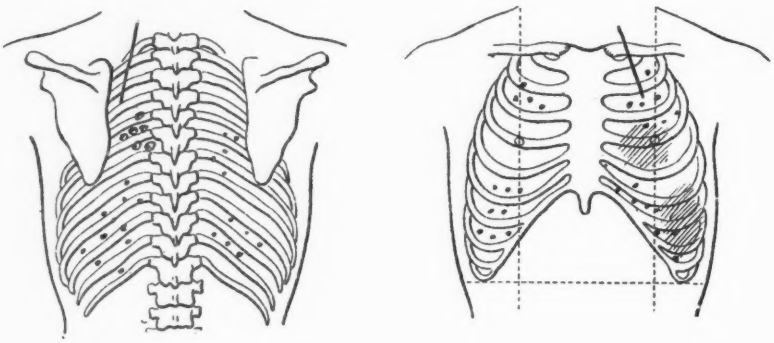


FIG. 8. May 11, 08. Since attending his weight had decreased from 10 stone to 9 stone 4 lb. His cough was much the same, but there was no haemoptysis. The murmur was only found in patches on the front of the left chest. Fixed râles were still present, and at the left lower apex there were some which moved on coughing. There was now distinct dullness over the left apex in front and behind, and the breath sounds over the whole chest were weaker than they had been.

accompanying figures, which show both development and subsidence, and its curious association with superficial fixed râles. In the diagrams the shaded areas indicate its distribution from week to week (Figs. 5, 6, 7, and 8).

*Case XV.* N. P., the case figured, aged 32, was admitted to Hospital on March 30, 1908, complaining of cough of seven to eight months' duration. Expectoration was abundant, and during the previous few weeks consisted chiefly of blood. The breath was short. There had been no wasting. He 'vomited' some blood three years ago. He had recently had pain in the chest, down the sternum, and radiating into the abdomen.

### RELATIONSHIP TO OTHER PHYSICAL SIGNS, ETC.

The results are summarized in the accompanying table, in which the numbers of the cases are given. It will be seen that—

11 cases gave a history of pleurisy.

4 exhibited coarse pleural friction.

2 showed pleuro-pericardial friction.

21 exhibited superficial fixed râles in the neighbourhood of, or in, the same locality as the occurrence of the murmur.

1 showed systolic intugging of the lower ribs.

9 had dullness at one or both bases.

36 had definite signs of involvement of one or both apices by tuberculosis.

| History of pleurisy. | Coarse friction. | Pleuro-pericardial friction. | Superficial fixed râles. | Systolic intugging of the ribs in left axilla. | Basal dullness. | Apical dullness, with or without diminished movement, weak or prolonged breath sounds, and loose râles. |
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| | | 48 | | | | |

Now an examination of this table, and the figures, directs attention to two relationships. The one the connexion of the physical sign with tuberculosis; the other a connexion with involvement of the pleura. Before proceeding further it may be well to lay stress on two considerations. In the first place it

must not be forgotten that the statistics were compiled at a chest hospital at which a large percentage of the out-patients are tuberculous. In the second place attention must be directed to the physical sign given in the table as 'superficial fixed râles'. Under this heading râles, which give the impression of being heard at the end of the stethoscope, and which are unaffected by coughing or breathing, are placed. Occurring for the most part at the end of inspiration, and of a fine rustling character, or of a coarser quality and heard throughout the greater part of a respiratory cycle, usually either widely scattered over the chest, or confined to the edges of the pleural cavity, they are taken as evidence of affection of the pleura. Whether such an assumption is justified may be largely a matter of opinion; but the statement of their quality is in any case imperative. Granting the assumption to be a fair one, the cases divide themselves naturally into the following classes:—

*Group I.* 24 cases in which there was unmistakable evidence of tuberculosis, and at the same time strong evidence in favour of pleural involvement (Cases 1, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, 17, 18, 21, 22, 24, 26, 28, 30, 32, 36, 39, 45, and 47). It is not proposed to consider these cases in further detail.

*Group II.* 12 cases in which there was strong evidence of a tuberculous lesion, but in which there were no signs of pleural involvement (Cases 2, 6, 19, 20, 25, 27, 29, 33, 34, 37, 40, and 46). These also require no further detailing.

*Group III.* Cases in which there was no evidence of tuberculosis, or in which sufficient evidence has so far been omitted (Cases 3, 7, 16, 23, 31, 35, 38, 41, 42, 43, 44, and 48). These require further consideration and may be again subdivided.

*Sub-group* (*a*). 2 cases in which, though there was no special dullness, moist râles were brought out by coughing (Cases 23 and 35). The following are the relevant facts:—

*Case* 23. History of pleurisy eight years previously. Cough one week; prolonged expiration at both apices; fixed râles of left apex; additional râles at left apex on coughing. Developed apical dullness.

*Case* 35. Cough with brisk haemoptysis on two occasions a week before attending. Râles at left apex on coughing. Base of heart somewhat uncovered and pleuro-pericardial friction. Ceased attending.

*Sub-group* (*b*). Cases in which apical lesion was doubtful or ill-defined, but in which there were suggestive symptoms or signs. The subdivision contains all the remainder with one exception (Sub-group (*c*), Case 38).

*Case* 3. Attending for general weakness and slight cough. Hip-joint trouble fourteen years ago (old sinuses). Prolonged expiration at both apices. Ceased attending.

*Case* 7. Cough and shortness of breath, two years. Apices not clear, but no definite dullness. Condition stationary for eight weeks. Ceased attending.

*Case* 16. Cough and expectoration over six months. Wasting; shortness of breath. Superficial fixed râles in left axilla and at apex of left lower lobe, where there was also friction. Ceased attending.

*Case* 31. 'Congestion of lungs' twelve years ago. Cough and expectoration three months. Expiration harsh at both apices. Improved.

*Case* 41. Pleurisy three years ago. Cough and expectoration (blood-streaked) one month. Voiceless one month. Wasting. Larynx congested. Improved.

*Case* 42. Attending for anaemia five months. Haemoptysis (clots) three years ago, on several occasions. Cough. Apices not clear. Superficial fixed râles left base. Improved.

*Case* 43. No cough. Brisk haemoptysis on four occasions. Expiration prolonged and resonance increased at both apices. Improved.

*Case* 48. Expectoration two to three years. Brought up blood-clots recently. Wasting. Occasional moist râle at apex of lower lobe in left side. Improved.

*Sub-group* (*c*). *Case* 38. Double aortic disease of rheumatic origin. Regurgitation free. Left heart much hypertrophied. Superficial crepitations at both bases and in left axilla.

It will be seen that the majority of cases of Group III are either definitely tuberculous or are at the least under suspicion. Case 38 is the only one of the whole series in which tuberculosis can be excluded. A few of the other cases of the group are, however, very indefinite.

## Remarks.

It is not proposed to enter upon a detailed discussion of this series of cases or of their bearing upon the value of the cardio-respiratory murmur. The material is in many respects incomplete, and is not sufficiently abundant to allow of any very precise conclusions. The need for caution is more strongly felt, as the opinion is entertained that the forty-eight cases do not in every respect offer a fair sample of patients, and that the cardio-respiratory murmur is met, unaccompanied with physical signs in the chest other than a rapid and somewhat forcible heart-beat, in a larger proportion of non-tuberculous subjects than the statistics collected would seem to indicate. At the same time, the writer is impressed with its value as a physical sign in out-patient work, and has found it a useful guide to the frequent re-examination of many patients. Henssen has analysed a number of cases of the same kind. In 268 patients he found the sign in 39, or 14·5 per cent.; 27 of the 39 cases had the tubercle bacillus in the sputum. In 88 youths from a military school, he found the sign in four cases. Two of these, he states, were suspected of tuberculosis. The remaining two were robust and had no other physical signs in the chest. Both gave a history of left-sided pneumonia. The observations made during the present investigations are in agreement in many respects with those of Squire.

In conclusion, there appears to be a remarkable frequency of the physical

sign in pulmonary tuberculosis, and more particularly in those forms in which the pleura is extensively involved; yet further observations are required, and more especially upon patients of nervous constitution, in whom excitement readily raises the force and frequency of the heart-beat, or upon healthy subjects after strenuous exercise.

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# THE PRODROMAL RASHES OF SMALL-POX

(With an account of the Literature of the Subject from the earliest times till the present day)

By the late R. S. THOMSON and JOHN BROWNLEE

With Plates 9–11

## Introductory.

The opportunities of studying small-pox afforded by the prevalence of that disease in Glasgow at intervals during the past ten years have resulted in our becoming familiar with that interesting group of small-pox eruptions commonly known as 'initial' or 'prodromal'. These develop during the prodromal stage, that is to say, during the period prior to the appearance of the characteristic papules. It is not easy to determine the precise proportion of cases in which these eruptions occur, on account of the fact that patients suffering from small-pox are usually not brought under notice of the physician till the more evanescent prodromal rashes have completely disappeared. For the same reason some uncertainty must exist as to the precise time during the prodromal stage of small-pox at which these eruptions first show themselves; but it seems probable that the latter part of the first or the second day is the most frequent period of their appearance. Opportunity, however, was occasionally afforded for the early study of these rashes by the admission of patients to hospital from the City Reception Houses where contacts are kept under close medical supervision. The date of disappearance of these rashes can be more easily determined. Some are evanescent, fading before or soon after the first appearance of the true eruption; but slight traces of the less evanescent varieties of this group may sometimes be found as late as the end of the first week of illness. Others are more persistent, and may frequently be observed undergoing a process of development when the patient comes under observation on the third day of illness or even later, and the last traces of certain of these may still be present well on in convalescence.

Prodromal eruptions vary greatly in the seat of their distribution; some covering the whole body, while others are present over limited areas only. They vary also in appearance, and sometimes two and rarely three different forms are found coincidently in the same individual.

As this group of eruptions is somewhat complex, the subject will be made clearer to the reader if we discuss the various prodromal rashes in detail. We shall first deal with the individual eruptions, namely, the prevariolar erythemata,

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the petechioid, the petechial, vesicular, and bullous eruptions, and finally with the various combinations of these.

*Prevariolar Erythemata.*

1. *General Erythemata.* (*a*) *Scarlatiniform.* (Plate 9, Figs. 1 and 2.) Probably the most common of the initial rashes is that which presents itself as a more or less uniform erythema, covering the whole of the body. When examined in detail on its first appearance this erythema is seen to consist of minute maculae closely set together, between which the skin presents an erythematous blush much paler than that seen in the maculae themselves. These maculae, which are not larger than an exceedingly small pin-head, resemble in colour the paler varieties of the scarlet fever rash, and are little if at all elevated above the surrounding skin. This rash in most cases extends over the whole body, including the face. It is sometimes perfectly uniform in colour, but the depth of tint may vary over different parts, being sometimes moderately bright where the skin is soft, as over the arms, front of elbows, and forearms, in the groins, and over the inside of the thighs, while elsewhere it is so pale as to be readily overlooked on a cursory examination. When faint, this eruption is best seen in a subdued light. A variety of this form is that in which the continuity of the erythema is broken by small patches of skin from which the rash is completely or almost completely absent. This, which is represented in Plate 9, Fig. 2, may be regarded as a transitional form between the uniform erythema first described and that having a distinctly measly character. When the patient comes early under observation both these erythemata are seen to develop first on the back, chest, and arms, spreading to the legs somewhat later. The maculae at the extending margin are generally larger than elsewhere. This uniform erythema is frequently evanescent; but sometimes it is more persistent, and, especially when the true eruption is very sparse, the last traces may not disappear till the seventh or eight day of illness. There can be no doubt that it is much more commonly seen in cases of small-pox modified by vaccination, and, according to older writers, in inoculated small-pox, though it is exceptionally present in cases of the unmodified disease. Of sixty-nine vaccinated persons showing a general scarlatiniform prodrome the true eruption became confluent in six, and of these one died. The majority of the others suffered from a very mild attack. In unvaccinated persons this variety of prodrome seems to warrant a much graver prognosis than when the patient is vaccinated, for of four persons in whom it was observed, two died.

(*b*) *Morbilliform.* By this name we are in the habit of designating a group of eruptions in which the erythema when fully developed occurs in patches varying in size from a millet seed to that of a split pea or larger. In their earlier stage these eruptions consist of small red points not larger than a pin-head, separated by areas of skin presenting a pale erythematous blush. These points appear at first more or less uniformly, but later, groups of them coalesce to form irregular patches separated by a much paler erythema in which a few

small red points may still be seen. When these scattered red points are absent the skin between the patches is much clearer, and the whole surface presents a somewhat measly appearance. (Plate 9, Fig. 3.) The erythematous patches may be larger than those just described, often elongated, especially when seen on the sides of the chest and flanks, and commonly elevated above the surrounding skin, though less so than in true measles. (Plate 9, Fig. 4.) Commonly this eruption has a close resemblance to the somewhat modified true measles rash so frequently seen in adults, in which the erythematous patches are smaller and less elevated than is usual in children. Exceptionally the erythematous patches are more elevated, and so closely resemble the characteristic measles eruption of childhood, both to the eye and touch, that a differential diagnosis without a careful consideration of all the symptoms is practically impossible. Of this variety we have seen but one example.

The intensity of this erythema varies greatly; being in some cases moderately vivid and in others so pale as to be visible only in a subdued light. Occasionally it has a slightly purplish tint.

The distribution is similar to that of the uniform erythemata, but there is less variation in depth of colour over different parts of the body. It not infrequently appears on the face. In the case referred to above, in which the eruption was indistinguishable from that of measles, the patches were larger and elevated in that situation.

The experience of the Glasgow Hospital is that these macular rashes are not commonly seen in cases where the true eruption subsequently becomes semi-confluent or confluent, so that their presence would seem to warrant a favourable prognosis. A study of the table will show that of twenty-five vaccinated persons presenting a general macular erythema, two suffered from a confluent attack and neither died. This rash was observed in one unvaccinated child, aged three years, in whom the after-following eruption was discrete, who made a good recovery.

(*c*) *Erysipelatous or Astacoid Erythemata.* Among the older writers the initial rash, which we here designate erysipelatous or astacoid, was variously referred to as scarlatiniform, morbilliform, and erysipelatous, and was one of the earliest of this class of eruptions described in the literature of small-pox. Their familiarity with the appearances presented by this eruption or rash was probably due to the fact that it is more common among unprotected persons, such as the oldest of our writers had to deal with, than among persons protected by inoculation or vaccination. This rash is but exceptionally general in its distribution, and we therefore reserve the detailed description to the section on local erythemata.

(*d*) *Livid Erythemata.* In a small proportion of cases the whole surface is covered by a deep erythema, interrupted by broad streaks and bands of purple, the combination imparting a dark plum colour to the skin. This eruption will be best appreciated by a reference to Plate 10, Fig. 5, in which the appearance described is successfully represented. This eruption, which we have observed only in unvaccinated persons, is distributed over the trunk and limbs, but not

on the face. It seems to be present in the most malignant forms of the disease only, and is probably an exaggerated variety of the astacoid eruption. All the cases which came within our experience died during the first week of illness.

(*e*) *Urticaria.* Some observers have described an urticarial variety of prodromal rash, in which the wheals closely resemble those of true nettle-rash. No example of this has come under our notice in small-pox, though we have observed similar eruptions at the onset of other specific fevers, such as scarlet fever and measles.

All the forms of erythema described so far, except the last, are free from irritation. They disappear on pressure, leaving behind a yellowish staining of the skin which, generally speaking, varies in tint in proportion to the depth of the erythema. In the case of the uniform erythemata this coloration may persist for several days after the eruption has disappeared. The staining is deepest in the case of the plum-coloured and astacoid rashes, the skin appearing of a deep gamboge yellow when the erythema is dispersed by pressure.

2. *Local Erythemata.* In addition to the erythemata just described, which may involve the whole trunk and limbs, and sometimes the face, we have to consider a group of similar eruptions which present a more local distribution.

(*a*) *Pale simple Erythemata.* Of these, two varieties are met with, the uniform roseolar and the morbilliform. Both of these affect the same situations, appearing more especially over the lower part of the abdomen, groins, and flanks, occasionally extending to the axillae, and other selected portions of the body. Their distribution may be more local than this, and may be limited to the axillae, to the skin over the inner aspect of the arms, to the forearms, the legs below the knees, and exceptionally to the region of the nipples. These areas of distribution may be combined in a variety of ways. Simon describes an extensor distribution of these local erythemata, and especially their appearances over the olecranon, extensor surfaces of the forearms and hands, the knees, the patellae, and the inner aspect of the feet, where the rash is commonly limited externally by the tendon of the extensor longus hallucis. This last distribution is, according to Simon, very suggestive of small-pox. While admitting the possible truth of Simon's extensor distribution, our experience does not lead us to attach the same importance to it as was given by that writer. This very limited distribution we have seen only when the patients came under our notice while the true rash was in an early papular stage, for when an opportunity was afforded of tracing more extensively distributed initial erythemata from the first appearance till their complete disappearance from the skin, it was found that the extensor situations assigned by Simon were precisely those in which this erythema was the last to develop and fade. Several writers who describe these very limited erythemata admit that the patients were seen by them somewhat late in the attack.

(*b*) *Capnitoid* (Gr. καπνός, smoke) *Erythemata.* By this name we would designate a form of local erythema not, so far as we know, hitherto described. It is commonly limited to the lower part of the abdomen and groins, but may extend slightly backwards over the lumbar regions. It is bounded above by an

irregular line passing horizontally between the anterior superior spines of the ilia, while below it merges into the pigmented skin of the genitalia and upper thighs. This erythema, as the name we have adopted indicates, presents a somewhat pale or sepia tint, the affected skin being slightly darker or more livid than that in the neighbourhood. It varies considerably in intensity, being at times quite distinct, while in other cases it is detected only on the closest scrutiny and in subdued light. It disappears on pressure, leaving behind a faint yellowish staining such as is commonly found after the dispersion by pressure of the slight prodromal erythemata. This eruption is not elevated and seems absolutely uniform. It is probably one of the commoner of the prodromal rashes. It is very evanescent, but it is often overlooked unless distinctly marked. It is found, as far as we have seen, mostly in vaccinated persons, and warrants a favourable prognosis. Only nine cases of this type of rash are noted in the table, but this is undoubtedly far short of the actual numbers observed. One of the patients in whom it occurred was an unvaccinated child of nine months, who made a good recovery.

(*c*) *Erysipelatoid or Astacoid* (Gr. ἀστακός, a lobster) *Erythemata.* The area of distribution of this erythema is practically the same as that of the more widely distributed local erythemata. It is frequently limited to the groins; sometimes it extends from below Poupart's ligament upwards and backwards, involving the flanks; and in others, again, it reaches as high as the axillae on both sides, spreading inwards under the clavicles. The upper part of the back, chest, and abdomen usually escape, but isolated patches of erythema in these situations are not infrequent. This eruption may reach downwards over the thighs. Rarely it covers the whole of the body, but is usually more intense over the forearms and legs, where it may present the appearance of a dusky scarlatiniform rash. When this eruption is present elsewhere the hands and feet are occasionally intensely affected, and the upper margin of the congested skin is sharply defined a little distance above the wrists and ankles. It has been stated by certain observers that this eruption usually involves the face as well as the parts just mentioned, but this does not agree with our experience. In certain cases of haemorrhagic small-pox the erysipelatoid eruption may appear upon the face, but it is more commonly absent, the face in such cases being the seat, not of a true erysipelatoid prodromal rash, but of a puffy congestion which may be mistaken for it.

On its first appearance this rash consists of innumerable small red points of the size of a small pinhead, but not infrequently larger. Later these become confluent to a considerable extent, when the rash presents a deep lobster-red colour which is uniform over the confluent portion. At the edges this uniformity of colour is to some extent lost, the marginal zone being broken up by bands and areas of skin free from erythema, and beyond this isolated spots, varying in size from a large pin-head to a split pea, are commonly seen. These isolated spots are best seen along the lower margin of the rash as it extends downwards over the thighs. Sometimes, however, the extending margin is sharply defined and presents no straggling areas of congested skin. This is best seen in those cases in which this rash is limited to the lower parts of the trunk and upper

parts of the thighs. The intensity of the colour varies, the affected parts being sometimes of a brilliant red. In other cases the redness is deeper and more dusky, while between these innumerable grades of coloration exist. In Plate 10, Figs. 6 and 7, the colour is that usually seen in the more limited varieties of this erythema. When widely distributed the tint is generally less brilliant than when it is limited, and the distinctly livid tint, frequently seen in the latter case, is then not at all common.

It has sometimes been described as a haemorrhagic rash, but with this class of eruption it possesses in reality nothing in common. Firm pressure with a slip of glass will completely dispel the erythema, when the skin will be seen either of a uniform deep yellow colour or covered with small brownish yellow maculae like pale freckles, an appearance which suggests the staining sometimes seen after measles rather than that caused by an eruption of blood into the skin. A general stippling which persists throughout the yellow staining is frequently observed. This rash is sometimes accompanied by a variable number of small petechiae.

This erysipelatoid eruption is markedly elevated above the unaffected skin, a condition which is more obvious in cases where the rash is limited than in those in which it is widely spread, though probably this difference is more apparent than real. The swelling is partly the result of active cutaneous congestion and partly of oedema, the latter condition probably differentiating the rash from the milder forms of erythema in which the changes in the skin are almost if not entirely due to active congestion, and this suggestion is to some extent supported by the fact that in persons in whom the astacoid eruption is present an oedematous condition of the conjunctivae is not infrequently associated with it. When the hands and feet are affected the swelling is often very marked. This rash warrants a very grave prognosis, and usually ushers in a confluent or haemorrhagic attack of smallpox which generally ends fatally. The only case of an unmixed astacoid prodroma noted in this table died. Itching is unusual, but occasionally the patient complains of tingling of the part affected.

3. *'Petechioid' Eruptions.* (Plate 9, Fig. 4, Plate 10, Fig. 8, and Plate 11, Fig. 10.) Occupying a position intermediate between the local macular erythemata and the true haemorrhagic prodromal rashes is one to which in this Hospital it has been customary to apply the term 'petechioid'. This rash is composed of numerous maculae, varying in size from a small pin-head to that of a hempseed. The colour varies considerably in different individuals, and even in the same individual maculae may similarly vary in colour. Usually they have the appearance of small yellowish or reddish brown freckles, but frequently some of them are larger and present a faint violet tint. They do not completely fade on pressure, but leave behind faint greenish yellow points which would seem to represent the central portion of the maculae, the marginal parts of which are dissipated; for on removing the pressure the original colour is gradually restored. The maculae are therefore not true haemorrhages the result of rupture of blood-vessels, but are partly congestive and partly the result of diapedesis through

weakened capillaries. Sections through the affected skin show no evidence of extravasation of blood.

This eruption is commonly first seen in the course of the second day of illness, when the majority of the maculae are reddish brown or violet; later the red colour is to a large extent lost, the yellowish brown tint becoming predominant. The process of development may occupy several days, continuing in progress for some time after the appearance of the true eruption, and the last traces may not vanish till the patient is beginning to show signs of convalescence; frequently, however, the maculae just described develop and fade within the compass of two or three days.

The usual seat of election of this eruption is the skin over the lower part of the abdomen and groins. Sometimes the distribution is very characteristic, the maculae being arranged in the form of an irregular inguinal triangle of Simon, the apex of which, when the thighs are approximated, lies about midway between the knees and the arch of the pubis. The outer sides are formed by irregular lines running obliquely upwards and outwards towards the great trochanters, from which they ascend almost vertically till they reach the anterior superior spines of the ilia. The base is formed by an irregular line running between the anterior superior iliac spines and having its centre a little below the umbilicus. Not infrequently this eruption ascends over the flanks, broadening out towards the axillae to form an axillary triangle. This triangle sometimes extends inwards under the clavicles. Within the triangles described the maculae are closely set, but at the margins they become more scattered. The larger and purplish tinted spots referred to above, which are never so numerous as the others, are grouped mainly within the inguinal triangle.

In a small number of cases the yellowish brown maculae compose the whole of the eruption, when the rash is found principally over the lower part of the abdomen and groins and over the flanks and lumbar region between the lower ribs and the iliac crest. Rarely it is more limited and may be present only in the popliteal spaces, over the flexures of the elbows or beneath the mammae. It is also seen in situations exposed to irritation, such as round the neck, the wrists, and immediately below the knees, though this has much less to do with deciding the locality of the rash than in the case of the true small-pox eruption.

This eruption is usually strikingly symmetrical, but at times the symmetry is to some extent lost, and even when it appears upon the trunk it may be more distinct, both as regards the number of maculae and the intensity, on one side than on the other.

The widely distributed varieties of this rash are frequently associated with a more or less vivid erythema which may involve not only the seat of election of the petechioid rash but the face and limbs as well. When this erythema is intense (astacoid, *vide supra*) the maculae are sometimes obscured by its presence, but may be rendered more prominent on dispelling the congestion by pressure. The erythema always disappears before the maculae, and when this occurs these are seen to stand out without an erythematous base.

When there is a decided erythema in such cases the macular portion of the eruption may extend downwards well over the thighs and legs, and in two cases which came under our observation the petechioid eruption involved the whole body and limbs but was obscured by a deep purplish erythema.

This association of an erythema with a macular rash has given rise to the name 'petechio-erythematous', under which this eruption is described by some authors; but as already indicated these maculae are probably not really haemorrhagic in origin and must be distinguished from true petechiae which occasionally appear during the prodromal stage of small-pox.

It has been frequently observed that the characteristic eruption of small-pox avoids the area over which this prodromal rash commonly appears, and occasionally a confluent variolous eruption may be observed to terminate abruptly when it reaches the edge of the area occupied by this prodrome. This is not invariably the case, for while the true eruption is frequently altogether absent from these situations, yet sometimes they present a very sparse and exceptionally even a confluent eruption. It must be remembered that the abdomen and upper parts of the thighs are situations rather avoided by the true small-pox rash, and it is by no means uncommon to find practically no true eruption in these situations, even in semiconfluent and confluent cases, though its absence has not been preceded by a prodromal rash of this type. Besides, we have not infrequently observed an abundant true eruption in the popliteal spaces, with practically none over the lower part of the abdomen and inner aspect of the thighs, though the prodrome had been originally present in all these situations.

When this eruption consists of yellowish brown maculae distributed over the lower part of the abdomen, flanks, and loins, the prognosis is by no means grave, and we have occasionally seen cases in which the after-following true eruption consisted of not more than a dozen papules. An equally favourable prognosis is warranted when the eruption consists of similar maculae and is limited to small portions of the skin or is the result of irritation. When on the other hand this eruption consists of spots having a deep red or purplish tint, more especially when associated with the astacoid erythema, the prognosis is grave, the after-following eruption being frequently confluent or even haemorrhagic. Of all varieties of petechioid prodrome occurring alone twenty-eight cases are registered in the table, of whom only one was unvaccinated. Of the vaccinated, six passed through a confluent attack of small-pox, and two died, in one of whom the eruption was abundant and in the other confluent. The unvaccinated patient who presented a very sparse eruption made a good recovery.

4. *Petechial Eruptions.* (Plate 11, Fig. 9.) In small-pox of a malignant type the characteristic eruption is sometimes preceded by a rash of true haemorrhages, which vary in size from a split pea downwards. They do not appear simultaneously, and consequently the different petechiae may present shades of colour varying between red and a deep purplish black. They occupy several days in their development, and at their height are sharply demarcated from the surrounding skin and sometimes slightly elevated, but as they fade the margins

become less defined, and in those patients who recover the petechiae pass through all the colour-changes of an ordinary haemorrhage, though the smallest haemorrhages, which are commonly about the size of a pin-head and of a brilliant red colour, mostly retain their brightness for some days and then change to a dirty yellow. They differ clinically from the large ecchymoses sometimes seen later in malignant cases. They are usually irregularly scattered over the trunk and limbs and vary in number from two or three up to many hundreds. At times they are collected principally over the lower part of the abdomen and inner sides of the thighs, where they form a roughly triangular grouping resembling the arrangement described above.

The significance of this eruption is usually serious, and so far as our experience goes most cases presenting it end fatally. Exceptionally, however, cases are met with in which the after-following true eruption indicates a comparatively mild attack and recovery takes place, a circumstance perhaps explained by the fact that the occurrence of these haemorrhages is sometimes apparently determined by irritation resulting from the bites of vermin or from poultices and other local applications. Of the three cases of this noted in the table one was haemorrhagic, two confluent, and two died.

5. *Vesicular Eruptions.* (Plate 11, Fig. 10.) In a certain proportion of cases where a petechioid prodromal rash exists a number of minute vesicles about the size of a pin-head are found associated with it. These are moderately firm to the touch, slightly opalescent, and most frequently found over the groins above Poupart's ligament. Their number is usually small. We have never observed them apart from the petechioid eruption, and they seem in no way to modify the prognostic significance of that rash. These vesicles differ clinically from sudamina, but we have not examined their contents microscopically.

6. *Bullar Eruptions.* Very exceptionally the true small-pox eruption is preceded by or its first appearance associated with a very sparse eruption of bullae varying in size from a large pea to a hazel-nut. This eruption we have seen in some three or four cases only, and in each case it was situated on the face or neck. The bullae contain a slightly opalescent fluid, which yields an abundant growth of staphylococcus aureus when inoculated on suitable culture media. Microscopically the fluid presents a few leucocytes. These bullae differ from those of ordinary pemphigus in so far as they show no tendency to recur, the whole cycle of changes being completed in two or three days. In none of the cases which came under our notice were there more than three or four bullae. It is impossible to form any opinion regarding the prognostic value of this rash, but it may be worth observing that in every instance within our knowledge it was associated with an exceedingly mild and modified attack of the disease.

### *Composite Prodromal Rashes.*

While all the eruptions described above, with the exception, perhaps, of the vesicular, may appear singly, certain of these are more commonly found associated. Most frequently the paler erythemata (whether uniform or macular,

scarlatiniform and morbilliform) appear alone; but it is not uncommon for these prodromata, and especially the more deeply coloured varieties, to be associated with a true 'petechioid' rash of the usual distribution, in which situations the basal erythema is apt to be more intense than elsewhere. When associated with the paler erythemata the petechioid rash consists merely of reddish brown spots, and purplish or violet coloured maculae are practically never present. This combination is found most commonly in persons to some extent protected by vaccination, and even when most marked generally warrants a favourable prognosis. The prognostic value of this combination is borne out by a study of the table, for of twenty-eight cases occurring in vaccinated persons only four were confluent and one died. Among the older writers there seems to be some difference of opinion as to the value of this composite prodromal rash from the standpoint of prognosis, but this is probably to be explained on the ground that much confusion existed between this particular combination and that so frequently seen in malignant small-pox, in which the intensely red 'astacoid' rash is associated with a petechioid eruption of purple or violet coloured maculae. There can be no doubt, however, that the combined erythematous and petechioid rashes are of a more grave prognostic significance than the erythemata alone. Of the twenty-eight cases recorded in the table fifteen showed a 'confluent' or 'very abundant' small-pox eruption and one died.

The erysipelatoid or astacoid rash, whether general or local, frequently occurs by itself, but within our own experience it more commonly appears along with other forms of prodromata. It is often associated with a pale scarlatiniform or morbilliform erythema, covering the forearms and legs, and in addition a petechioid rash, more especially that variety in which the majority of the maculae tend to be of a deep red or violet colour, is frequently combined with these. When associated in this way the petechioid rash may be very abundant and follows its usual distribution, as already described. In very malignant cases of small-pox the prodromal stage is not infrequently characterized by the presence of a general or local astacoid rash accompanied by a more or less abundant crop of true petechiae, the latter being in most cases collected largely in the crural triangle. In the other cases these petechiae are scattered irregularly over the body, but are generally most abundant in those parts where the astacoid rash is present. In persons who have been vaccinated but who have almost completely lost their immunity numerous 'petechioid' maculae are also occasionally found along with the true haemorrhages, and these, like petechiae, are present principally over their usual seats of election. Very exceptionally the vesicular prodromal eruption described above is found in company with the petechioid and petechial rashes when these are set upon an astacoid base. Speaking generally, the true erysipelatoid or astacoid rash warrants a serious prognosis, and the gravity of this increases if it be associated with petechioid spots, but still more if it co-exists with true petechiae. Within our experience an erysipelatoid or astacoid rash almost invariably ushers in a semiconfluent or confluent attack of small-pox, and the same statement holds if it be associated with petechioid maculae.

A certain though small proportion of such cases recover, but when this rash is associated with the true petechiae in addition to the petechioid maculae the prognosis is of the worst possible kind, the patient commonly dying towards the end of the first week with haemorrhages from the mucous membranes and into the skin. In ten cases given in the table, of whom seven were vaccinated and three doubtfully so, all died. The presence of a vesicular initial rash along with this combination does not apparently in any way modify the prognosis.

The 'petechioid' prodrome is not infrequently unassociated with any other form of initial rash, but commonly it is accompanied with one or more of the varieties which we have already described, and its prognostic value seems to depend largely upon the character of the co-existing prodrome. Occasionally it is found in company with one of the milder scarlatiniform or morbilliform erythemata, when it is not infrequently limited to the regions of the groin and other flexures, but it is sometimes associated with a local or general astacoid rash and occasionally with minute vesicles.

The distribution of the petechioid rash when associated with others is generally speaking the same as that which it assumes when it occurs by itself, but it is much more limited when associated with the milder erythemata than when associated with an astacoid rash. In the latter case the petechioid maculae are often very numerous, involving the greater part of the inguinal triangle and the trunk, and in such cases the rash is not infrequently accompanied by true petechiae. Sometimes numerous initial haemorrhages are scattered over the area of distribution of the petechioid rash without any other rash or prodrome being present. A favourable prognosis is apparently always warranted when the paler erythemata and petechioid eruptions are found in conjunction, but when associated with the astacoid the prognosis is always grave, and mostly fatal when true haemorrhages are present.

True petechiae are frequently observed without an accompanying rash of another kind, but they are commonly found associated with the petechioid or the erysipelatoid rash, or these three varieties of prodromal eruption may co-exist. This petechial eruption usually accompanies the livid erythema to which reference has already been made. The vesicular eruption is most commonly associated with the petechioid. The pemphigoid eruption we have seen accompanied by a pale rose erythema.

### *Period of Occurrence.*

As has been already remarked it is by no means easy to determine the exact period in the prodromal stage at which the initial rashes first appear, owing to the fact that patients as a rule are not brought under observation till the presence of the true eruption suggests the nature of the illness from which they are suffering.

No doubt the system of segregating contacts in reception houses or similar institutions might afford a considerable amount of evidence on this point were it not that revaccination is so vigorously pursued by the authorities that the

number of contacts who subsequently develop small-pox is too small to afford a basis for purposes of generalization. Nevertheless the number of cases admitted to hospital during the prodromal stage is sufficient to furnish us with some information as to the relative period of appearance of the different varieties of rash, though not sufficient to warrant a dogmatic statement.

The majority of these rashes seem first to show themselves about the end of the first or in the course of the second day of illness, and the erythemata, both local and general, seem to appear and attain their full development most commonly within this period. This, however, is not invariably the case, at least with the local erythemata and especially with the erysipelatous variety, for not infrequently these are found to increase both in intensity and in area of distribution after the patient is well on in the papular stage of the true eruption.

The petechioid and the true petechial eruptions are undoubtedly first observed towards the end of the second or in the course of the third day of illness, yet judging from the rate of development of these rashes there seems ground for believing that they not infrequently appear earlier. Like the local erythemata they may continue to develop after the appearance of the true rash.

The vesicular eruption probably appears coincidently with the 'petechioid', without which, so far as our experience goes, it is never present.

The pemphigoid eruption probably appears early; at least, in the examples of this eruption which have come under our notice the bullae were fully developed when the patients were first seen in the early papular stage of the true rash.

### *Age of Prevalence.*

The prevariolar rashes are found most commonly in patients who contract small-pox between puberty and middle life. In childhood these eruptions as a whole are rare, but occasionally one of the prodromal varieties of erythema (scarlatiniform, morbilliform, or capnitoid) may be found even in very young children. Examples of the 'petechioid' and petechial rashes have not come under our notice under the age of thirteen or fourteen years. Beyond the period of middle life these eruptions diminish in frequency, and we have not observed them among very old people. (See tables.)

The erysipelatoid, 'petechioid,' and petechial forms of eruption occur most commonly after the age of thirty, that is to say at a period when patients who have been vaccinated in infancy only are losing the protection of their acquired immunity.

In view of the close resemblance which exists between small-pox and chicken-pox, it is natural to expect that the prevaricellar eruption so commonly present even in very young children suffering from the latter disease would be represented by prevariolar eruptions at corresponding ages in vaccinated children suffering from small-pox. This, however, is not the case, as has already been stated. The explanation lies possibly in the fact that though prevariolar rashes are much more common among vaccinated than among unvaccinated persons,

yet small-pox in vaccinated children is a rare disease, so that opportunities for observation are comparatively few.

The number of persons admitted to the Hospital at Belvidere during the past ten years who have contracted small-pox after revaccination or were found to be suffering from a second attack of the disease was relatively very small, and in none of these was a prodromal rash present on admission, nor could any information on this point be elicited from the patients.

In conclusion it may be stated that the experience of this Hospital regarding the relative frequency of prevariolar rashes in different epidemics corresponds with that of previous observers, for while in the epidemic 1892–5 these were comparatively uncommon, in the last epidemic prevalence of the disease, 1900–2, they were very frequently observed.

## A Review of the Literature.

As already stated prevariolar eruptions occur occasionally in unvaccinated persons, very commonly indeed in persons who have been vaccinated, and to judge from some of the older medical writings they occur by no means infrequently in inoculated small-pox. It will be convenient, therefore, to divide our discussion of the history of these eruptions into three periods. The first period will include all the available references from the time of Rhazes till the introduction of inoculation into this country. The second period will include all references in medical literature dealing with prodromal rashes observed while the operation of inoculation for small-pox was commonly practised, while under the third will be discussed all references to these rashes from the introduction of vaccination by Jenner to the present day.

*Section I.* The earliest reference in literature is possibly to be found in the works of Rhazes, probably written during the earlier part of the tenth century, though the writer's meaning is obscure, and is differently given in the Latin and English translations. In the latter Rhazes states: 'Sometimes the small-pox sinks inwards and is so like the measles that it is afterwards said that the measles are turned into the small-pox.' This quotation suggests the disappearance of a measly prodromal rash, such as is found to precede the true eruption of small-pox, rather than the development of a measly-like papular small-pox rash into characteristic papules and vesicles. The Latin version differs in meaning and is as follows: 'Aliquando apparent Variolae similes Blactiis et aliquis medicus dixit quod Blactiae vertuntur in Variolas.' The paragraph of which this extract is a part suggests a moderate frequency of the condition described, a fact which is rather against the theory that the reference is to a prodromal rash, in so far as measly prodromal eruptions in unprotected individuals are distinctly rare. The statement may, however, refer to a patchy or measly astacoid rash.

Sydenham's statement is more precise and unequivocal than that of Rhazes. He says: 'Variolae dictae (confluentes) nunc erysipelatis ritu nunc morbillorum erumpunt, a quibus non nisi a Medico in his morbis versatissimo distinguuntur

saltem quoad faciem externam.' There can be little doubt that the breaking out of confluent small-pox in the resemblance of erysipelas refers to the fact that an erysipelatous or astacoid rash sometimes precedes the appearance of the true small-pox eruption, more especially in severe cases, while the latter part of the paragraph almost certainly refers to the measly appearance so frequently presented on its first eruption by the true rash.

A similar astacoid or erysipelatous eruption is described by Morton associated with black spots and petechiae: 'Universa cutis, in instanti quasi, rubedine saturata et profunda perfusa, erysipelatosi tumoris ad instar (maculis nigris hic illic interspersis) cum aequali superficie quadantenus crassescit; quam quidem erysipelatosam rubedinem cutis per triduum eruptionis integrum retinet.' He also says: 'Efflorescentia confluens et ubique rubedine saturata more febris scarlatinae vel erysipelatosae universam fere cutim perfundens cum petechiis intermixtis mortem ultra secundum maturationis diem nulla medicorum arte posse protelari significat.' In addition to this several cases are recorded in which this eruption was present (Cases 37, 38, and 39). In some of these the eruption seems to have been uniformly distributed, while in others it occurred in patches like measles on the chest and limbs, but was uniform over the face. Haemorrhagic spots were associated in all the cases with this rash and these varied apparently both in size and colour, being in some cases black, while in situations where the haemorrhages were small they presented a red colour. As might have been anticipated from a more modern knowledge of this variety of prodrome all the cases proved fatal. Robert Walker, though writing in 1790, deals only with natural small-pox and describes several prodromal eruptions known to the physicians of his day. On page 140 he says: 'The eruption is commonly preceded by a fiery red rash or efflorescence which shows itself on the face, neck, and breast, and sometimes extends over the whole body. It appears towards the close of the second or beginning of the third day, and from which in the course of some hours the pimples emerge.' The description given here leaves no doubt that the writer refers to the erysipelatous prodromal eruption. In the same volume (page 149 et seq.), he refers to what is apparently a haemorrhagic eruption, and in the course of his remarks says: 'In some cases they [the petechiae] commence with the eruption of pimples or even before them'; and further: 'The mild and most favourable are those of a faint red colour, which kind are generally late in their appearance.' This latter quotation may refer either to a haemorrhagic prodrome or to haemorrhages occurring coincidently with the appearance of the true rash or immediately after it. Such petechial spots when prodomal, if we are correct in this opinion as to their character, usually change to a brown rather than to a purplish tint, and appear early rather than late in the disease.

*Section II.* Up to this point the references quoted refer to cases of small-pox in which the disease was contracted in the usual manner (natural small-pox). After the introduction of inoculation from the East the references to prodromal rashes are more numerous; and it is generally admitted by the older writers that

inoculated small-pox is more frequently associated with prodromal rashes than ordinary small-pox. Baron Dimsdale deals with the subject at some length. He describes in inoculated small-pox the roseolar eruption (erysipelatous efflorescence), both local and general, points out variations in degree and intensity of the roseola, and draws attention to the fact that these are commonly associated with a very sparsely distributed true eruption. 'If it [erysipelatous efflorescence] shows itself on the skin partially here and there, it is not very alarming, and soon wears off. But sometimes the whole surface of the skin is covered with a rash intimately mixed with the variolous eruption, and so much resembling the most malignant kind of confluent small-pox as scarcely to be distinguished from it; and indeed some cases of this sort have happened where being accompanied with petechiae and livid spots I have been much alarmed.... Besides, upon a careful examination there may sometimes be a few distinct pustules larger than the rest mixed with the rash which are the real small-pox.—After two or three days the skin from a florid changes to a dusky colour, a few pustules remain which advance probably to maturation without any further trouble ensuing from this formidable appearance.' It is probable that in this extract Baron Dimsdale intends to compare the vivid generalized roseola not with the appearance presented by a confluent variolous rash, but with the general 'astacoid' eruption with which no doubt he was familiar as ushering in a confluent or malignant attack of the disease. His reference to petechiae and livid spots which preceded a very sparse true eruption running on to maturity would suggest that he was familiar in inoculated small-pox with what we have called the 'petechioid' variety of prodrome, and if we are correct in this interpretation of his observation it is of great interest to find that prodromes bearing these characters occurred in persons partially protected by inoculation, just as they occur at present in persons partially protected by vaccination.

Willan in discussing prodromal rashes says: 'In the natural small-pox I have occasionally observed an appearance of the *roseola variolosa* on the third or fourth day, and with a small and favourable eruption of pustules; but I am informed by those who must have had better opportunities of observing than myself that this appearance is much more rare in the natural than in the inoculated small-pox.' In evidence of this statement he gives, on the authority of his resident, Wachsel, a summary of 346 cases of inoculated small-pox, in 23, or 1 in 15, of which roseolar prodromal eruptions were observed. 'It appears ... on the second day of the eruption, which is generally the ninth or tenth after inoculation. The efflorescence is first observable on the arms, breast, and face; on the following day it spreads over the trunk and extremities, in some cases it spreads into contiguous arches, in others it is in longitudinal irregular patches with small distinct dots intermixed,' and in a few cases, 'all these appearances being combined, it forms an almost continuous redness all over the body. Several parts of the rash are a little elevated about the surface as in measles. When a universal efflorescence of a dark red colour takes place, with a violent eruptive fever immediately before the variolous pustules, we have reason to



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expect a confluent eruption and a fatal termination of the disease.' This extract requires no comment, for it is clear that 'universal efflorescence of a dark red colour' is the usual erysipelatous or astacoid prodrome which warrants always a grave and generally a fatal prognosis. In addition to what we have quoted this author gives detailed excerpts of the literature dealing with this subject prior to the publication of his own work. It is perhaps only just to Willan and his assistant Wachsel to observe that subsequent writers have quoted both the foregoing figures and description without any acknowledgement of their sources of information, and even the name *roseola variolosa*, which, so far as we can discover, was originally applied by Willan to this initial rash, has been erroneously ascribed to later writers.

*Section III.* Bateman, evidently quoting Willan's experience, states that about one case out of every fifteen of inoculated small-pox presents the *roseola variolosa*. His description of the efflorescence is to this effect: 'Its distribution is various, sometimes in oblong irregular patches, sometimes diffused with numerous interstices, and in a few cases it forms an almost continuous redness over the body, being in some parts slightly elevated.'

Thomas refers to a morbilliform eruption preceding confluent small-pox, but as the morbilliform or measly variety of prodrome probably always precedes a mild attack of variola it is legitimate to conclude that the eruption referred to by this writer is really what is now known as a patchy variety of the astacoid rash.

Rayer describes both the scarlatiniform and mobilliform prodromata, and refers briefly to erythemata presenting a macular character. He likewise refers somewhat vaguely to another prodromal eruption, probably the erysipelatous or astacoid form.

Gregory similarly expresses the opinion that roseolar and scarlatiniform prodromata are more frequently present in inoculated or vaccinated persons, and states that within his experience these eruptions sometimes occur in patches.

Though a considerable number of writers have referred to certain of the more common prodromal rashes found in small-pox, no other records of importance were published. Thus Erasmus Wilson mentions scarlatiniform and astacoid prodromata; Marson describes only the scarlatiniform erythemata, in spite of his increasingly large experience of small-pox. Liveing describes the scarlatinal prodromata, both local and general; Aitken, in addition to the scarlatiniform, refers to the astacoid and erythematous as well, while Niemeyer describes only the local and general scarlatiniform and measly prodromata.

From about the year 1860 till the present time a number of writers have by their careful observations extended our knowledge of these interesting rashes. Thus Wilks, besides referring to the erythemata, describes one case of what is clearly a 'petechioid eruption' in a vaccinated subject. The patient, a boy of fifteen years vaccinated in infancy, was seized with the usual symptoms of small-pox. 'The next day he had a roseolous rash on the body and legs which Stocker immediately suspected was the onset of variola. On the following

day the rash over the lower part of the abdomen had become petechial. After this the purpura faded away and the true variolar eruption appeared on the face and extremities. The disease ran its course in a mild manner, and the lad made a rapid recovery.' In addition, this writer quotes a case in which the hands, and to a less extent the feet, were swollen, and presented a colour such as might be produced by the action of logwood, the case subsequently running a mild course. We have never met with a local eruption answering to this description, though occasionally a general or violent astacoid rash may present a colour answering to Wilks's description. Such cases are usually of the severest type.

Hebra describes the *erythema variolosum* and the *roseola variolosa* as also the petechial prodrome, which, however, he does not distinguish clearly from the petechioid. With regard to the former or erythematous varieties he divides them into general and local, and describes the uniform as well as the macular forms suggestive respectively of scarlet fever and measles. This writer, for the first time, so far as we are aware, points out the triangular configuration of certain of the initial rashes when they appear on the lower part of the abdomen and the inner aspects of the thighs. 'The rash invariably remains confined to a space bounded above by an imaginary line drawn transversely across the umbilicus at the sides by the lumbar regions, and below by a line traced across both thighs, about three finger breadths above the knees. It extends also further outwards in the inguinal region than lower down towards the knees; so that, when the thighs are pressed together, the area occupied by the rash forms a triangle with apex directed downwards.' This author does not draw any distinction, so far as description goes, between the different forms of erythemata or roseola, but that he was evidently familiar with both 'astacoid' and 'petechioid' rashes is shown by the following passage: 'These cases [i. e. those with inguinal rash] do, however, more often terminate badly than in recovery, and particularly when the affection passes beyond mere hyperaemia into haemorrhage, when, in fact, a purpura rather than an erythema shows itself on the abdomen and on the thighs in the stadium prodromorum' of variola. This statement can only be regarded as correct if it applies to the astacoid haemorrhagic or deeply livid erythema, for there can be no doubt that the simple form of erythema, whether morbilliform or scarlatiniform, always warrants a favourable prognosis, even when it occupies the triangular space described above.

Trousseau describes the morbilliform, scarlatiniform, and 'petechioid' eruptions, and his description suggests that he was familiar with the astacoid rash as well. He was evidently familiar with the difference between the haemorrhagic prodromata and that we describe as 'petechioid' when associated with a patchy scarlatiniform efflorescence. 'The spots are small, of a more or less deep red colour, sometimes blackish, nearly always running into each other so as to form large patches, haemorrhagic looking, to which the English have given the name of *rash*. These haemorrhagic scarlatiniform eruptions, which in natural small-pox constitute an alarming symptom, do not lead to an unfavourable prognosis in modified small-pox. They generally show themselves

in the groins, on the thighs, and on the lower part of the abdomen. They do not disappear on pressure, or at least there remains a greenish yellow mark which quickly acquires the reddish hue of a more or less violet shade momentarily effaced by the pressure of the finger.' While hesitating to criticize the description given by so distinguished a clinician as Trousseau, yet it may be pointed out that though apparently familiar both with the astacoid and the scarlatiniform varieties of prodromata, he does not draw a sufficiently clear distinction between the astacoid and the more intense or deeply coloured erythemata, for an astacoid rash, even when it appears in a vaccinated subject, is probably always an indication that that person has lost his original protection, and consequently its presence warrants a very grave prognosis indeed.

Simon has written one of the most important papers upon the subject, but unfortunately we have not been able to see the original, and are indebted to synopses for our knowledge of its contents. He describes the erythematous and macular rashes, and also notes the definite localization of these and of the 'petechioid' rashes. He also has given his name to the crural triangle referred to on page 193, and to the extensor distribution of the rash described on page 190; and he describes the distribution of 'petechioid' rashes as frequently seen in the axilla.

Sheby-buch, following Simon, refers to a number of prodromal rashes, but he limits the name to those which are associated with haemorrhage and does not regard the erythematous varieties as strictly speaking prodromata of small-pox. He draws no distinction, however, between petechial and the more evanescent petechioid eruptions, and he gives no detailed account of their seats of election, though he regards petechial prodromata over the lower abdomen and inguinal triangle as of evil import.

Curschman refers to scarlatiniform, measly, 'petechioid,' and true petechial prodromata, and to the erysipelatoid or 'astacoid' rash, which he describes as frequently associated with haemorrhagic spots. His account is fairly full and detailed, and he refers at some length to the results of other observers' work.

Mackey describes the petechial, 'petechioid,' and the erythematous varieties of the prodromal rashes, and he considers the last of favourable prognostic significance. He also quotes cases where a local astacoid prodrome was present over the abdomen and upper parts of the thighs; this he declares does not fade on pressure, and always suggests a malignant type of the disease.

Cross records two cases in which an erythematous rash appeared before the true eruption. In one case the rash occupied the flanks and loins, in the second it appeared in the axillary regions. This rash gradually became livid, but later it disappeared, the normal colour of the skin being restored, a condition attained in the first case on the eighth day. It is not easy to conclude from his description the precise nature of this prodrome, but judging from its distribution and the change in colour the rash in both cases was probably 'petechio-erythematous or petechioid'.

Sharkey narrates a number of cases in which prodromata preceded the

appearance of the true small-pox rash, giving examples of the scarlatiniform, morbilliform, and haemorrhagic prevariolar rashes. He does not draw any distinction between the milder scarlatiniform *roseola variolosa* and the more malignant astacoid rash. He draws a distinction between the petechioid, in which he states the spots pass from a reddish to a brownish colour, and the 'blue petechial' prodrome, and he likewise draws a clear distinction between these haemorrhagic spots which appear before and those which appear after the third day of illness.

In *Notes on Small-pox* by Osler, a paper we have not seen, he records the results of observations which, so far as we can infer, are in general agreement with those of his contemporaries. In his textbook in Medicine, his descriptions are much the same as those of other writers, but he specially mentions the plum-coloured rash sometimes seen in very malignant cases and also the urticarial form.

McNeill gives one of the most detailed accounts of these rashes published up to date of his own paper. He reviews the literature and gives a description of most of the known prodromals of small-pox, including the petechio-erythematous ('petechioid'), true haemorrhagic or petechial, and most of the erythematous varieties. The author likewise discusses at some length the diagnostic and prognostic significance of the varieties of these initial rashes.

McCombie describes most of the types of prodromal rashes in considerable detail, and specially notes, so far as we are aware, for the first time, the vesicular prodrome.

Roger and Weil describe erythematous, morbilliform, urticarial, and scarlatiniform prodromata. These, they state, may be either general or local, disappearing on pressure, leaving in some cases small points behind, which do not completely vanish. In addition they describe all haemorrhagic prodromata under the name of purpuric as well as the so-called erysipelatous prodrome, to which they give the name of astacoid (*ἀστακός*, a lobster). These authors tabulate their cases and deal with the frequency, duration, and prognostic significance of the different prodromal rashes.

Immermann quotes largely from earlier writers, but gives to some extent his own experiences of these rashes. He describes the erythematous morbilliform, astacoid, petechioid, and petechial prodromata. His localization is that of Simon, with whom he is in agreement both as regards the prognostic significance of these rashes as well as the relationship to subsequent distribution of the true variolar eruption.

In addition to the authors quoted descriptions more or less detailed are given by the writers of various textbooks in Dermatology and General Medicine—McCall Anderson, *Diseases of the Skin*; Flint, *Principles and Practice of Medicine*; Fagge, *Principles and Practice of Medicine*; Bristowe, *Theory and Practice of Medicine*; Moore, *Eruptive and Continued Fevers*; Allchin, *Manual of Medicine*; Tilbury Fox, *Skin Diseases*, &c.

*Section IV.* The earlier authors from whom we have quoted deserve considerable credit for the clearness with which they recognized the essential

characters of the initial rashes and the relation which these bear to the true eruption. This is more especially so in the cases of Morton, Dimsdale, Walker, and Willan, whose descriptions of the initial rashes with which they deal are perfectly clear and given in considerable detail. These authors likewise describe their distribution or seats of election, and to some extent their prognostic significance.

In spite of these writers' descriptions, however, a considerable body of physicians writing during the eighteenth and first half of the nineteenth century seem to have misinterpreted the appearances presented, especially by the roseolar and morbilliform initial rashes, and many cases are recorded during this period of patients suffering from variola with concurrent scarlet fever or measles. It must be admitted that so far as can be gathered in certain cases, and more especially in those where the roseolar and morbilliform rashes appeared after the true small-pox eruption, the writers had good ground for believing that their patients were suffering from two concurrent diseases, yet in those cases in which the initial rash referred to appeared shortly before the true small-pox eruption and disappeared before the latter had reached maturity, there is every probability that the cases described were really examples of small-pox occurring in persons partly protected by previous inoculation or vaccination, or in whom the natural immunity was great.

In a treatise by Ant. Sidobre the author records two cases which came within his knowledge and that of his uncle in which small-pox and measles appeared simultaneously—'aliquando etiam variolae et morbilli simul aegros afficiunt et intermiscentur,' &c.; it is reasonable to suppose, seeing the disease appeared simultaneously and apparently ran a concurrent course, that the morbilliform eruption was in reality not true measles but a measly prodrome. It is impossible to conclude whether the prodrome referred to by this author was astacoid in its character, but as recovery is recorded to have taken place in at least one case it is possible that the initial rash may have been one of the less severe measles type.

In a description of the last illness of Queen Mary II by Walter Harris that writer states that at first some doubt existed in the minds of the physicians whether the royal patient was suffering from measles or small-pox, or both, and a little further on in his description he says, 'Die octavo latae Morbillorum maculae in pectore permanebant,' &c. This statement that measly spots were present on certain parts of the body on the eighth day with the true small-pox rash, when taken in conjunction with the doubt expressed of the nature of the disease at the outset of the illness, makes it perfectly clear that the queen was the subject of a morbilliform prodromal rash which her physicians' further description enables us to recognize as being probably astacoid in character. On the face this eruption was uniform, and, as is common with this variety of eruption, it was associated with petechiae from an early period in the attack. From the heading of the chapter ('De variolis anomalis sive cum morbillis consociatis'), and several other short passages in his account of the case, it would seem that in

the opinion of the author the queen's death was the result of associated or concurrent measles and small-pox.

De Haen, describing concurrent attacks of small-pox and measles, observes 'imo ut ambo simul eodem in subiecto efflorescant'. A case quoted in support of this statement is of special interest: 'Puerulus anni unius 22 Maii 1748. Febre morbillosa corripiebatur et die 25 Morbilli prodiere sed brevi adeo conferti ut nunquam magis. Verum circa os pustulae minimae instar nascentium Variolarum comparuere. Die 26 inter densissimos Morbillos toto corpore diffusos duodecim variolae in facie binaeque utraque in manu prodiere, foveam in medio habentis albidioris ac circulo rubro in ambitu ornatae.' The writer evidently regards this as an attack of measles immediately preceding the appearance of the small-pox eruption; but while admitting the possibility of this interpretation of these attacks, it is more reasonable to regard the first or primary rash not as measles but as a prodromal rash having measly characters. The mildness of the small-pox attack is in favour of a simple measly prodrome, and not of an astacoid prodrome with patchy distribution. In the *Ratio Medendi* the same author refers to a number of cases in which measles and small-pox were conjoined, and while some of these seem authentic, the first case referred to is more suggestive of a scarlatinal prodrome rather than of associated scarlatina and small-pox. The author says, 'Unica sane in puella Scarlatinas efflorescentias habuimus et Miliaria et Variolas. Scriptores Medicos consulentes, eorum qui id ita credant, offendimus plures. Suspendo tamen sententiam,' &c.

Russell narrates two cases of what he believed to be examples of coincident measles and small-pox occurring in the same individual. In one case, a female aged two, and in the second, a boy aged three, measly eruptions were found associated with the true small-pox rash. In the former, the measly and small-pox rashes were present on the fourth day, when the measly rash was very distinct, while in the latter case the measly eruption was faint on the third day of the patient's illness. There seems no reason to doubt that the measly eruption, which was in both cases preceded by a mild attack of variola, was an ordinary morbilliform prodrome, and not a measles rash.

Baudelocque describes a case which he considered an example of associated small-pox and scarlet fever, and states further that he is familiar with this association, as he had cases of both diseases in his hospital. An analysis of the case described suggests that it was in reality an example of an astacoid rash occurring in the course of haemorrhagic small-pox.

Barnes describes a case in which the small-pox eruption was preceded by a rash which in the observer's opinion was that of scarlet fever, but this eruption was so suspiciously like a scarlatiniform prodrome that, in spite of the fact that a case of scarlet fever occurred in the same household twelve days later with anasarca on the twenty-sixth day of illness, we are disposed to regard the former small-pox with 'scarlatina variolosa'.

Glehn reported to the St. Petersburg Medical Society a case which in his opinion was one of scarlet fever preceding modified small-pox, but in this

case also it is clear that the supposed scarlatinal eruption was in reality a prodrome.

Gallwey refers to similar cases, and records a case of measles and small-pox and one of scarlet fever and small-pox. It seems probable that the latter at least was in reality an astacoid eruption preceding a severe attack of small-pox with a delayed true rash.

Murchison collates a number of the preceding to which he adds several coming within his own experience. Some were undoubtedly examples of double diseases in so far as variola preceded the associated disease; but in others, in which the true small-pox followed rapidly upon the former, it is reasonable to suppose that, in a proportion of these cases at any rate, the associated eruption was really a prodrome. Thus in Cases I and IV the true variola was preceded by what was evidently a scarlatinal prodrome; while Cases III and V were undoubtedly examples of haemorrhagic small-pox with an astacoid prodrome.

Criticism of a similar kind might be passed upon cases of a like nature recorded by Cruickshanks, Ring, and Samson, and quoted by Aitken and others.

## APPENDIX.

NUMBER OF PERSONS SHOWING EACH VARIETY OF PRODROMAL RASH OUT OF 867 VACCINATED PERSONS SUFFERING FROM SMALL-POX, OF WHOM 38 DIED.

*'Erythematous' Prodromata. Vaccinated Cases—Males.*

| Age Periods. | Scarlatiniform. General. | | | | Scarlatiniform. Local. | | | | Morbilliform. General. | | | | Morbilliform. Local. | | | | Capnitoid. | | | | Totals. | | | | Total. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | C | D |
| 0–5 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5–10 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10–15 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 15–20 | 5 | 1 | | | | | | | | | | | | | | | | | | | 5 | 1 | | | 6 | |
| 20–25 | 5 | 1 | 2 | 1 | | 1 | | | 5 | 1 | | | 1 | 1 | 1 | | 1 | | | | 12 | 4 | 3 | 1 | 19 | 1 |
| 25–30 | 2 | 2 | | | 3 | 1 | | | | | | | | | | | 1 | | | | 6 | 3 | | | 9 | |
| 30–35 | 3 | 2 | | | | | | | 1 | 1 | 1 | | | | | | | 1 | | | 4 | 4 | 1 | | 9 | |
| 35–45 | 7 | 7 | 1 | | | 1 | | | 6 | 2 | 1 | | | 2 | 1 | | | | 1 | | 13 | 12 | 4 | | 29 | |
| 45–55 | 6 | 3 | | | | | 1 | 1 | 1 | | | | 1 | | | | 1 | | | | 9 | 3 | 1 | 1 | 13 | 1 |
| 55–65 | | | | | 1 | | | | | | | | | | | | | | | | 1 | | | | 1 | |
| 65–75 | | | | | | | | | | | | | 1 | | | | | | | | 1 | | | | 1 | |
| Total | 28 | 16 | 3 | 1 | 4 | 3 | 1 | 1 | 13 | 4 | 2 | | 3 | 3 | 2 | | 3 | 1 | 1 | | 51 | 27 | 9 | 2 | 87 | 2 |

Character of Rash.

S = Sparse. A = Abundant. C = Confluent. D = Death.

*'Erythematous' Prodromata. Vaccinated Cases—Females.*

| Age Periods. | Scarlatiniform. General. | | | | Scarlatiniform. Local. | | | | Morbilliform. General. | | | | Morbilliform. Local. | | | | Capnitoid. | | | | Total. | | | | Total. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | C | D |
| 0–5 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5–10 | | | | | | | | | 1 | | | | | | | | | | | | 1 | | | | 1 | |
| 10–15 | 1 | | | | | | | | 1 | | | | | | | | | | | | 2 | | | | 2 | |
| 15–20 | 1 | | 1 | | | 1 | | | | | | | | | | | | | | | 1 | 1 | 1 | | 3 | |
| 20–25 | 3 | | | | | | | | | | | | | | | | | | | | 3 | | | | 3 | |
| 25–30 | 3 | 2 | | | | 2 | | | 2 | 1 | | | 1 | | | | 1 | | | | 7 | 5 | | | 12 | |
| 30–35 | 1 | 2 | 1 | | 1 | | | | | | | | 1 | | | | 1 | | | | 4 | 2 | 1 | | 7 | |
| 35–45 | 2 | 1 | | | | | | | 1 | | | | 1 | | | | 1 | | | | 5 | 1 | | | 6 | |
| 45–55 | 1 | 1 | 1 | | 1 | | | | | | | | | | | | | | | | 2 | 1 | 1 | | 4 | |
| 55–65 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 65–75 | 1 | | | | | | | | | | | | | | | | | | | | 1 | | | | 1 | |
| Total | 13 | 6 | 3 | | 2 | 3 | | | 5 | 1 | | | 3 | | | | 3 | | | | 26 | 10 | 3 | | 39 | |

*'Petechioid' Prodromata. Vaccinated Cases—Males.*

| Age Periods. | Petechioid Rash alone. | | | | With general Scarlatiniform. | | | | With general Morbilliform. | | | | With local Scarlatiniform. | | | | With local Morbilliform. | | | | Total. | | | | Total. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | | |
| 0–5 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5–10 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10–15 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 15–20 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 20–25 | | 1 | | | 3 | | | | | 1 | | | 2 | 1 | | | | | | | 5 | 3 | | | 8 | |
| 25–30 | 2 | 1 | | | | 1 | | | 1 | | | | | 1 | | | | | | | 3 | 3 | | | 6 | |
| 30–35 | | 4 | 1 | | 1 | 2 | 1 | | 1 | | | | | | | | | | | | 2 | 6 | 2 | | 10 | |
| 35–45 | 2 | 2 | 1 | 1 | | 1 | | | | | | | 1 | | 1 | 1 | | | | | 3 | 3 | 2 | 2 | 8 | 2 |
| 45–55 | | 1 | | | 1 | | 1 | | 1 | | | | | | | | | | | | 2 | 1 | 1 | | 4 | |
| 55–65 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 65–75 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total | 4 | 9 | 2 | 1 | 5 | 4 | 2 | | 3 | 1 | | | 3 | 2 | 1 | 1 | | | | | 15 | 16 | 5 | 2 | 36 | 2 |

*'Petechioid' Prodromata. Vaccinated Cases—Females.*

| Age Periods. | Petechioid Rash alone. | | | | With general Scarlatini-form. | | | | With general Morbilli-form. | | | | With local Scarlatini-form. | | | | With local Morbilli-form. | | | | Total. | | | | Total. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | S | A | C | D | | |
| 0-5 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5-10 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10-15 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 15-20 | 1 | | | | | | | | | | | | | | | | | | | | 1 | | | | 1 | |
| 20-25 | | 1 | | | | | | | 1 | | | | | | | | 1 | | | | | 3 | | | 3 | |
| 25-30 | 1 | 2 | 1 | | | 1 | | | | | | | 1 | | | | 1 | | | | 3 | 3 | 1 | | 7 | |
| 30-35 | | | 2 | | | 1 | | | | | | | | | | | 1 | | 1 | | 1 | 1 | 3 | | 5 | |
| 35-45 | 1 | 1 | 1 | 1 | | | | | | | | | | | | | | | | | 1 | 1 | 1 | 1 | 3 | 1 |
| 45-55 | 1 | | | | | | | | | | | | | | | | | | | | 1 | | | | 1 | |
| 55-65 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 65-75 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total | 4 | 4 | 4 | 1 | | 2 | | | 1 | | | | 1 | | | | 2 | 1 | 1 | | 7 | 8 | 5 | 1 | 20 | 1 |

*'Astacoid and Petechial Rashes.' Vaccinated Cases—Males.*

| Age Periods. | Astacoid. | | Astacoid and Petechial. | | Astacoid with Petechial and 'Petechioid'. | | Petechial. | | |
|---|---|---|---|---|---|---|---|---|---|
| | C | D | H | D | H | D | C | H | D |
| 0-5 | | | | | | | | | |
| 5-10 | | | | | | | | | |
| 10-15 | | | | | | | | | |
| 15-20 | | | | | | | | | |
| 20-25 | | | | | | | | | |
| 25-30 | | | | | | | | | |
| 30-35 | 1 | 1 | 1 | 1 | | | 1 | | |
| 35-45 | | | 1 | 1 | | | | 1 | 1 |
| 45-55 | | | 1 | 1 | 1 | 1 | 1 | | 1 |
| 55-65 | | | | | | | | | |
| 65-75 | | | | | | | | | |
| Total | 1 | 1 | 3 | 3 | 1 | 1 | 2 | 1 | 2 |

Character of Rash.
C = Confluent. H = Haemorrhagic. D = Death.

*'Astacoid and Petechial Rashes.' Vaccinated Cases—Females.*

| Age Periods. | Astacoid. | | Astacoid and Petechial. | | Astacoid with Petechial and 'Petechioid'. | | Petechial. | | |
|---|---|---|---|---|---|---|---|---|---|
| | C | D | H | D | H | D | C | H | D |
| 0–5 | | | | | | | | | |
| 5–10 | | | | | | | | | |
| 10–15 | | | | | | | | | |
| 15–20 | | | | | | | | | |
| 20–25 | | | | | | | | | |
| 25–30 | | | 1 | 1 | | | | | |
| 30–35 | | | | | 1 | 1 | | | |
| 35–45 | | | 1 | 1 | | | | | |
| 45–55 | | | | | | | | | |
| 55–65 | | | | | | | | | |
| 65–75 | | | | | | | | | |
| Total | | | 2 | 2 | 1 | 1 | | | |

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## DESCRIPTION OF PLATES.

PLATE 9, FIG. 1. Prodromal rash: general erythema.
FIG. 2. Measly prodromal rash.
FIG. 3. Measly prodromal rash.
FIG. 4. Measly prodromal rash with petechioid spots.
PLATE 10, FIG. 5. Livid erythema.
FIG. 6. Astacoid erythema.
FIG. 7. Astacoid erythema.
FIG. 8. Petechioid eruption.
PLATE 11, FIG. 9. Petechial prodromal rash.
FIG. 10. Petechioid prodrome showing small vesicles.

2

4

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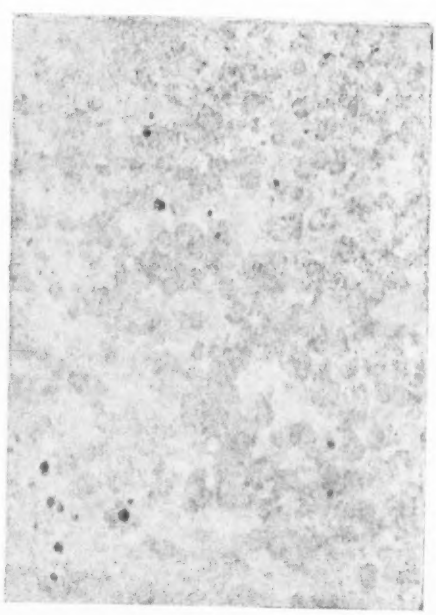

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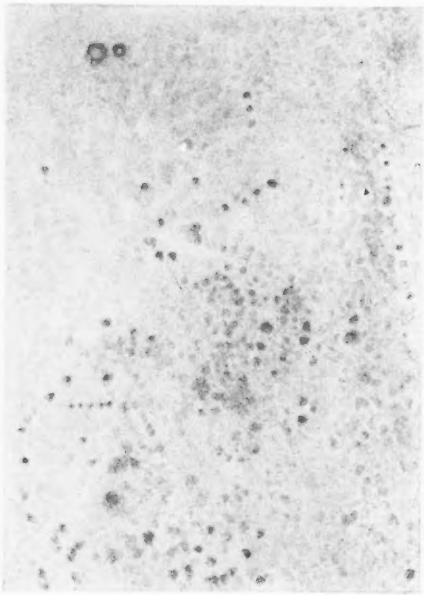

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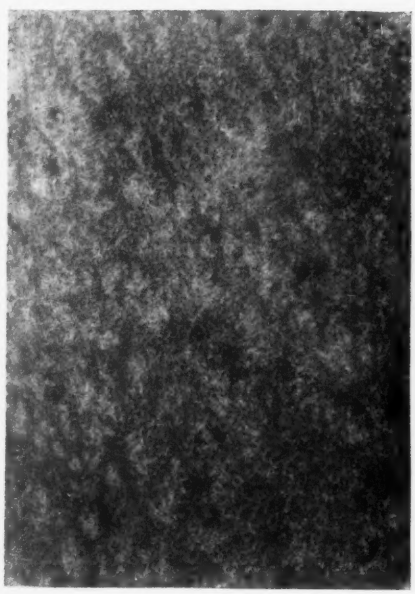

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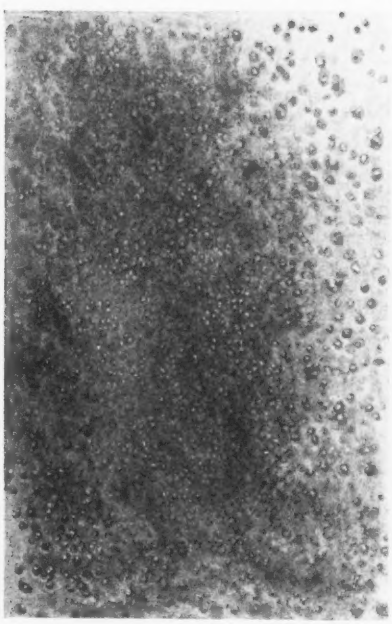

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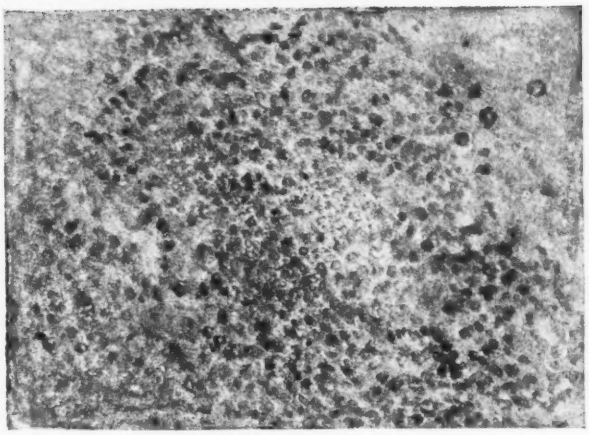

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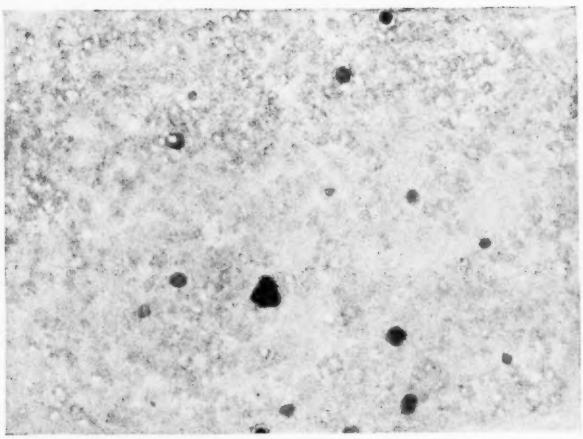

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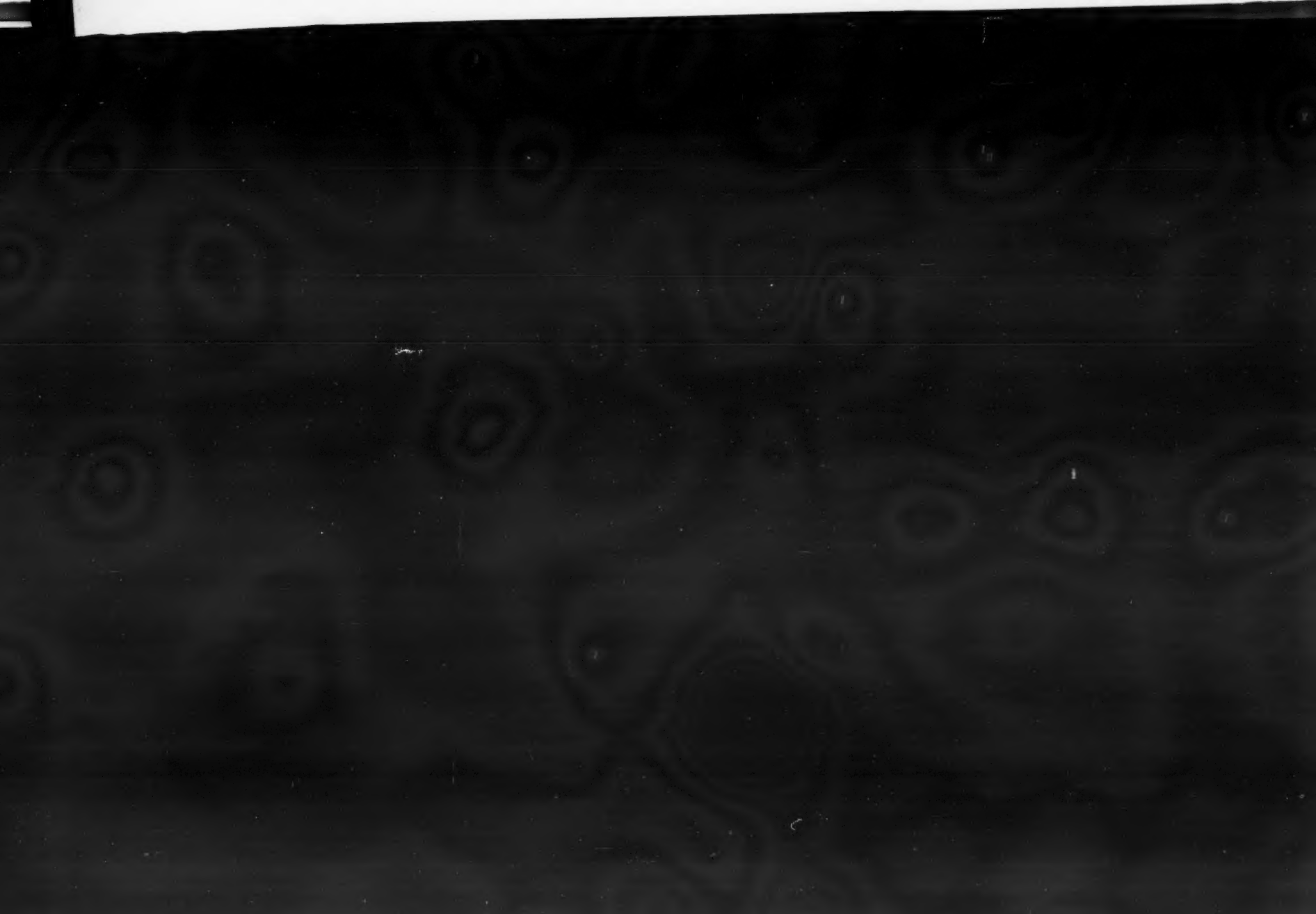


# THE SPEED-LIMIT OF THE HUMAN HEART

By ARTHUR F. HERTZ and GORDON W. GOODHART

With Plate 12.

Cardiac muscle is well known to differ from voluntary muscle in the comparatively long inhibitory period following its contraction, during which it cannot respond to stimulation of any kind. For this reason, if subjected to a rapid series of stimuli, it does not pass into a condition of tetanus like voluntary muscle, but contracts rhythmically at a rate which depends in each case on the exact length of the inhibitory period. The latter can be accurately estimated in the heart-muscle of cold-blooded animals, and the greatest possible rate at which it can contract can be readily ascertained by direct experiment. We are, however, aware of no observations which give any idea as to the maximum rate of the heart-beat in man. We have had under our observation for nearly a year a patient whose auricle we believe has been contracting at its speed-limit throughout this period. As the case has also other points of interest we will begin with a short description of the clinical history.

Rose B., aged 39, was admitted into Guy's Hospital on January 16, 1908. There was no history of rheumatism in her family and she was confident that she had never suffered from joint pains. She had scarlet fever when eleven years old, and shortly afterwards was troubled with palpitation, for which eight years later she attended Guy's Hospital as an out-patient. After treatment for two years she felt perfectly well, and remained so until 1902, when she again suffered from slight palpitation. In the autumn of 1907 for the first time she became short of breath, and in November she returned to the hospital as an out-patient. She was quite comfortable so long as she did not exert herself, and she was not orthopnoeic. Her lips were very cyanosed, but there was no oedema or enlargement of the liver. Her pulse was slow, weak and irregular, but the heart-sounds were so irregular and difficult to interpret that it was impossible to count them accurately; it was clear, however, that the rate of the pulse was only about one-half that of the heart-beats. The heart was only slightly enlarged. She refused to come into the hospital, so she was given Tinct. Digitalis three times a day and told to rest at home. A fortnight later the heart was more regular and a little slower, and a presystolic murmur could occasionally be heard. After this, however, she ceased to improve, the dyspnoea increased and the cyanosis became more general. The digitalis did not seem to suit her, so she was given nux vomica. On January 14, 1908, on getting out of bed she suddenly fell, but did not lose consciousness; she found that she had lost all power in her right side. She was admitted into the hospital the same evening.

On admission the patient was found to have an organic hemiplegia, the arm being more involved than the face and leg. There seemed no doubt that the paralysis was due to cerebral embolism. She complained of no discomfort, and, except for the hemiplegia, she was distinctly better than before Christmas. The cyanosis was less marked, and the liver, which was not tender, was only just palpable below the costal margin.

The cardiac impulse was in the fifth space, just outside the mid-clavicular line, and there was no cardiac dullness to the right of the sternum. The rhythm

of the heart was most frequently bigeminal, a strong beat, which produced obvious pulsation in the radial artery, being followed by a weak beat, which was impalpable at the periphery. The heart-sounds were still difficult to interpret, but it appeared that the first sound in the case of the stronger beats merged into a long systolic murmur, continuing almost up to the second sound, which was followed after a short pause by a diastolic murmur. The two sounds corresponding with the weak beat were not accompanied by murmurs. Sometimes (as shown in Fig. 2) the bigeminal rhythm gradually changed into a regular rhythm, which, however, only lasted for a short period.

The patient was given Tinct. Digitalis ♏ vij three times a day, and this was in a few days increased to ♏ x. On January 22 the pulse had dropped to 44, and although the heart-sounds were much the same in character, the pauses between them had become longer, and the patient felt somewhat uneasy. However, she slept soundly at night, and could lie quite flat with comfort. The digitalis was now omitted, and she had no more medicine during her stay in the hospital except nux vomica, which was given for a time without producing any noticeable effect on the heart, although the patient continued to improve subjectively. The heart was now generally regular, but it was still occasionally bigeminal in rhythm. The systolic murmur was constantly present, and the mid-diastolic was replaced by a presystolic murmur. Meanwhile the hemiplegia had almost disappeared, and when she left the hospital on April 6 she was able to walk slowly without discomfort.

After her discharge from the hospital she was seen regularly once a week at first and later once a fortnight until the end of October, except during August, when she was in the country. Her condition varied very little. She was able to get about in the house and walk the short distance to the tram and from the tram to the hospital without difficulty. She was always rather cyanosed, but there was never any oedema, and the quiet life she led prevented her from becoming dyspnoeic.

Between March 1 and October 30 numerous tracings were taken from the cardiac impulse and the jugular vein. Her pulse was always feeble, so sphygmographic tracings were taken only on a few occasions.

The jugular tracings always showed an exceedingly rapid but absolutely regular pulsation, which had no relation to the ventricular contractions, as indicated by the records obtained at the impulse. The jugular curve represented genuine auricular and not so-called fibrillary contractions, as on half a dozen occasions the contractions of the heart were watched with the X-rays, and it was seen that the auricle contracted at an exceedingly rapid speed, quite independently of the irregular and much slower ventricular contractions. In this connexion it may be noted that the contractions of the left auricle can rarely be seen with the X-rays, but that those of the right auricle can be easily compared with those of the left ventricle by the use of a horizontal very narrow diaphragm, just long enough to take in the borders of the right auricle on one side and the left ventricle on the other.

The wave produced by the auricular contractions was propagated as far as the retinal veins, in which rapid pulsations were seen by Mr. Eason, corresponding apparently in speed with those of the jugular vein.

*Effect of Atropine.* (Fig. 3.) Hypodermic injection of gr. $\frac{1}{100}$ of atropine sulphate had no effect on the auricle, and produced a hardly appreciable acceleration of the ventricle. Injection of gr. $\frac{1}{50}$ two days later had very

striking results. The jugular pulse showed not the slightest alteration in either the speed or the strength of the auricular contraction. On the other hand, the tracing obtained from the cardiac impulse showed that between seven and twelve minutes after the injection the ventricular contractions began to increase steadily in speed, their rhythm becoming regular instead of bigeminal, as it had been before the injection. The rate rose from between 78 and 84 to between 120 and 156. Two and a half hours after the injection the patient became breathless and giddy; no tracing was obtained, but the ventricular beat was timed with the stethoscope, and found to vary between 150 and 170. Soon afterwards it became gradually slower; four hours after the injection it had fallen to 102, and seventeen hours later it was 75—slower than immediately before the injection.

The acceleration of the ventricular beats after the injection of atropine must have been due to paralysis of the tonic vagal action. As the auricular beats were entirely unaffected, it is clear that the control of the auricle by the vagus must have been completely abolished.

Our case therefore differs essentially from ordinary cases of complete heart-block, as a number of observers (Erlanger, Gibson, Stengel, Doch, Finkelburg) have shown that in the latter condition the administration of atropine quickens the auricle, but has little, if any, effect on the ventricles.

There is little doubt that the patient's attack of scarlet fever was followed by endocarditis, which gave rise to mitral stenosis. It seems probable that the auricular muscle was at the same time involved, and that the vagal nerve-endings in the auricle were damaged beyond repair, whilst those in the ventricle were unaffected, so that the vagal control of the auricle had been completely lost, whilst that of the ventricle was still in a state of activity.

*Effect of Exercise.* (Fig. 4.) So long as the patient remained quietly in bed the rate of the auricle hardly varied from 234, and that of the ventricle only slightly from 80 a minute. It was found that posture had no effect on either the auricle or the ventricle, no change in the rate of either being produced on sitting up after the patient had been lying for some time or on lying down after sitting. The effect of exercise was observed for the first time after the patient had been in bed for 9 weeks. She sat up and lay down, repeating the movement rapidly about a dozen times. Not the smallest change occurred in the auricle as shown by the rate and size of the jugular waves. On the other hand the ventricle, which had been beating regularly for some time at an average rate of 7 times in each 5 seconds, immediately after the exercise beat 10, 9, and 9 times in consecutive periods of 5 seconds; then 8 times in two such periods after an interval of a quarter of a minute, and again after another 2 minutes. A few minutes later the speed had fallen to the original average of 7 beats for each 5 seconds. On a second occasion some days later similar records were obtained, the auricular beat being absolutely unaffected, whereas the ventricular beat rose from an average of 7 times in each 5 seconds to 12 immediately after the exercise, and then gradually fell to 7 again.

Later, when the patient was up, similar results were obtained by walking exercise, the auricle never showing the slightest alteration.

The normal acceleration of the heart after exercise is due mainly to inhibition of the vagus, possibly combined with stimulation of the sympathetic; this is partly a reflex from the active muscles and partly, especially at a later stage, a result of chemical stimulation of the medullary centres by products of metabolism, of which carbon dioxide is the most important. It is still uncertain whether these products of metabolism also act directly on the heart-muscle. The absence of any acceleration in the auricular rhythm after exercise in this case can thus be explained in the same way as the absence of any change following the injection of atropine, by assuming that the control of the auricle by the vagus is completely lost.

We were unable to demonstrate any change of speed in either the jugular or apical tracings produced by alterations in the respiratory rhythm or by holding the breath.

*The Constant Rapidity of the Auricular Contractions.* The most remarkable feature of the case is the extreme rapidity of the auricular contractions. On any given day we found the rate remained absolutely constant, but in the course of the ten months during which observations were made slight variations occurred from week to week, the rate having recently become more slow, but never less than 216. The effects of atropine and exercise show that the auricle was probably entirely free from nervous control. The absolute constancy of the rate under various conditions which gave rise to normal variations in the ventricular rhythm strongly suggests that the auricle had been beating throughout the period of observation at the fastest speed of which it was capable.

A small number of cases are on record, in which for a short period the heart has beaten at various rates between 200 and 300. But not many of these are reliable, as the rate was estimated by counting the pulse at the wrist or with the aid of the stethoscope placed over the cardiac impulse. Few observers will maintain that it is possible to count a pulse or heart-beat with any semblance of accuracy when the speed exceeds 200, even if the heart is beating regularly, and in the majority of such cases it is irregular. Balfour, in his *Clinical Lectures on Diseases of the Heart and Aorta*, wrote that he was himself unable to count a pulse beating over 150, and James Mackenzie, in his recent work on *Diseases of the Heart*, says that he suspects any estimates made of a pulse-rate over 200 unless graphically recorded, because he doubts if the human mind is capable of accurately distinguishing between events occurring at a speed of over 200 per minute. Dr. Bolton, however, tells us that he is convinced that the rapidity of the heart-sounds heard with a stethoscope was accurately estimated in a patient, who was in University College Hospital under Dr. Sidney Martin with acute cardiac dilatation, and in whom for a week the rate varied between 220 and 280. A few graphic records of a rate greater than 200 have, however, been made, such as 262 in Hay's case of paroxysmal tachycardia, and in one of Gibson's heart-block cases, in which the auricular rate rose to 275 after the

administration of atropine, while the ventricle remained unaffected. But we have found no graphic record of a heart beating at a rate of more than 200 per minute for any length of time, and the cases of extreme tachycardia with no graphic record were in most cases paroxysmal in nature. Even in the case under Dr. Sidney Martin the extreme tachycardia only lasted a week, and the condition of the patient with acute dilatation of the heart must have been very different from that of our patient, who has been comparatively well for most of the period of observation, as she has been up and performing her household duties for the last seven months.

Thus although there is no doubt that the human heart can beat for a short period at a greater rate than 236 per minute, which is the fastest recorded in our patient, there is no evidence that any heart could continue to beat for a considerable length of time at a speed much in excess of that. Individual variations must of course occur, but it seems probable that in our patient the greatest speed of which her auricle was capable was attained. It is easy to understand how this could vary with slight alterations in the quantity or quality of the cardiac blood-supply from week to week, as physiological experiments show that variations are produced in the refractory period of cardiac muscle under such conditions.

*Dissociation of Auricular and Ventricular Rhythm.* At no time during our observations has there been any association between the auricular and ventricular rhythm. This was particularly shown in the tracings which record the influence of atropine and exercise, as the acceleration in the ventricular rate and the subsequent return to normal occurred gradually and regularly instead of in jumps. There is no evidence to suggest that this dissociation is due to heart-block, the result of disease of the auriculo-ventricular bundle, and it appears more probable that the cause lies in the fact that the ventricle is physically incapable of keeping up with the rapid auricle, so that it is beating less quickly with a rhythm of its own.

In all cases of dissociation of the auricular and ventricular rhythm hitherto recorded the ventricular rate has been considerably slower than normal. James Mackenzie states that it rarely exceeds 32. The explanation generally given is that, owing to the complete block of the auricular contraction at the auriculo-ventricular ring, the ventricular muscle initiates a slow rhythm of its own. In the case here recorded the rate of the ventricle tends to be fast rather than slow, as it has varied between 72 and 120. It must therefore depend upon some other factor than the inherent rhythmic contractility of the ventricular muscle. We suggest that the auriculo-ventricular node and bundle are uninjured, and that it is in the former that the ventricular contraction is being initiated.

We have discussed the case with Mr. P. P. Laidlaw, Dr. James Mackenzie, Dr. Pembrey and Professor Gotch, to each of whom we are indebted for suggestions as to the interpretation of the records.

## DESCRIPTION OF FIGURES.

### PLATE 12.

FIG. 1. Tracing to show the bigeminal rhythm ; at rest.

FIG. 2. Tracing to illustrate the change from a bigeminal to a regular rhythm of the ventricle without alteration in the ventricular rhythm.

FIG. 3. Tracing to show the effects of atropin ($\frac{1}{50}$ gr. atropin sulphate subcutaneously).

FIG. 4. Tracing to show the effects of exercise.

In all the figures the upper tracing is the jugular pulse, the lower the apex beat; the time marker is below the tracing in Figs. 1 and 2, above it in Figs. 3 and 4.

Fig. 1

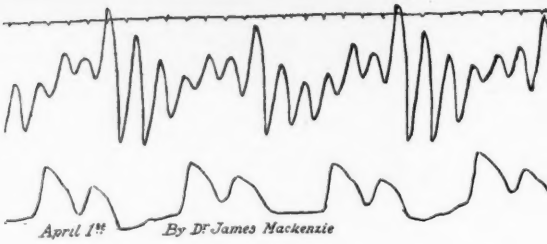



Fig. 2

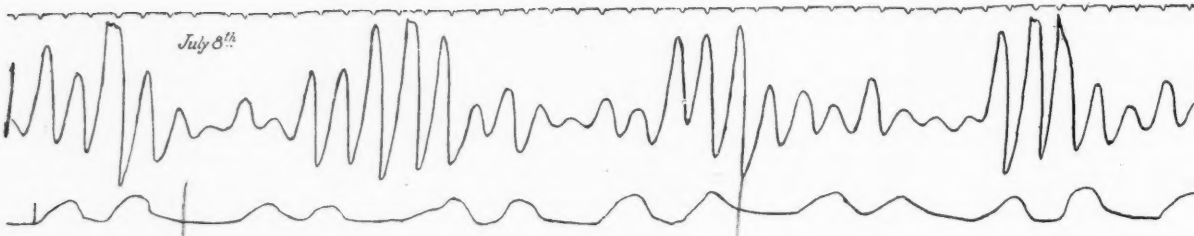



Fig. 3

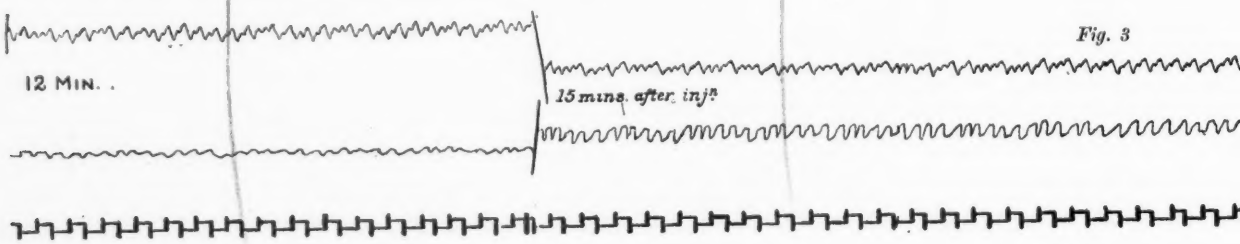



Fig. 3 (continued)

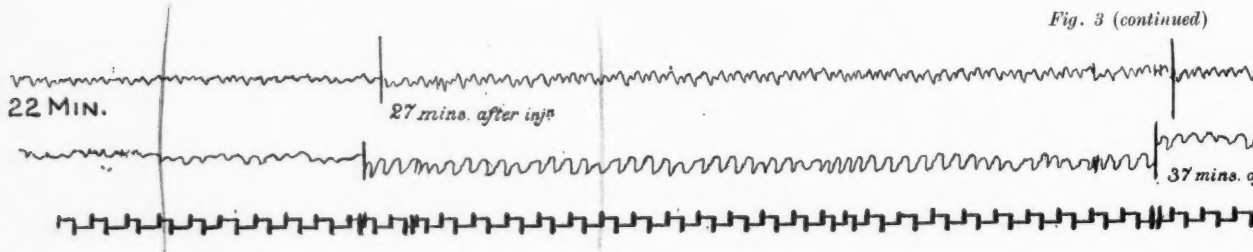



Fig. 3 (continued)

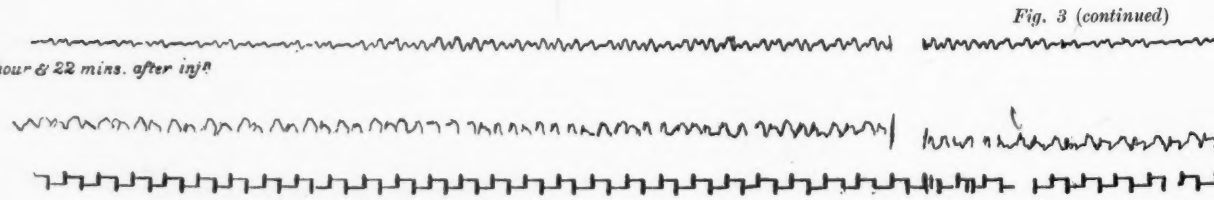
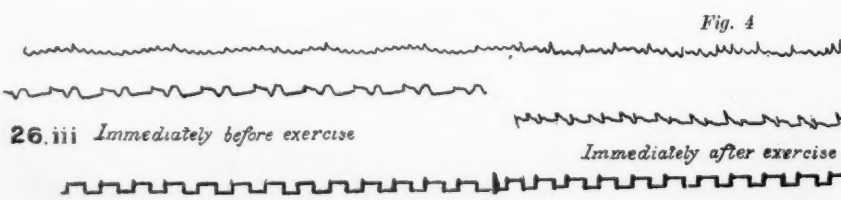
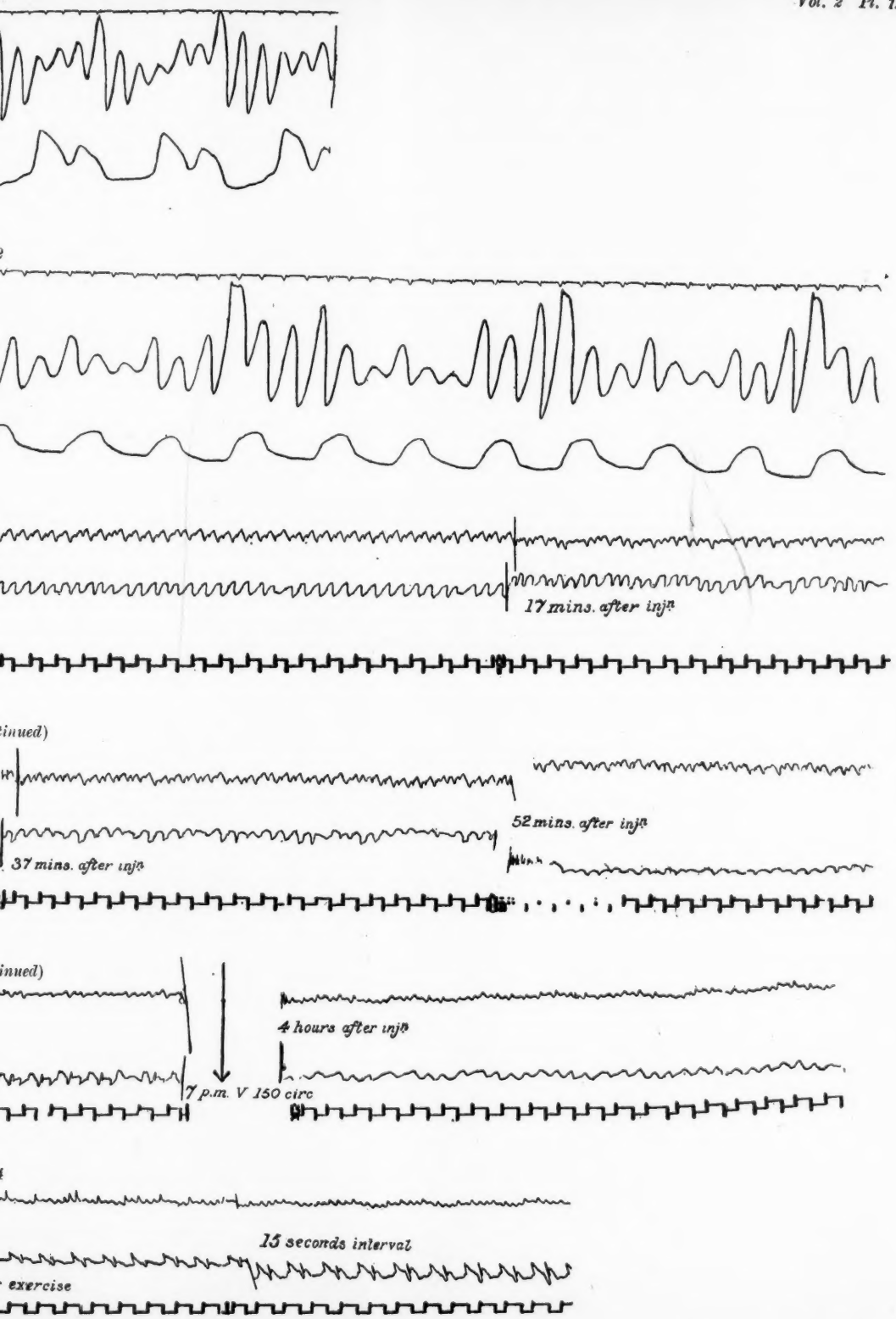



Fig. 4




17 mins. after inj.
52 mins. after inj.
37 mins. after inj.
4 hours after inj.
7 p.m. V 150 circ
15 seconds interval
exercise

# CHRONIC INFECTIOUS ENDOCARDITIS

By WILLIAM OSLER[1]

An endocarditis with fever as its only symptom may be prolonged for weeks or months under many different circumstances. Following rheumatic fever in a child an endocardial complication may keep up a temperature of from 100° to 101° for several months, during which time there may be no other symptoms and the general condition may remain fairly good. In chronic valvular disease in the stage of broken compensation slight irregular fever may persist for months, associated with the presence of fresh endocarditis. As a rule, the form of endocarditis to which we give the term infective, septic, or ulcerative runs its course under three months. That occasional instances were characterized by a very protracted course was noted by Wilks, Bristowe, Coupland, and Lancereaux. In my Goulstonian Lectures, 1885, I stated that this type had the following characteristics: the fever was irregular and intermittent, resembling ague; the cold, hot, and sweating stages might succeed each other with great regularity; in the intervals fever might be absent; two or three paroxysms could occur in the course of a day. In many of the instances the disease was prolonged to three or four months, and I give the notes of a case of Bristowe's, in which the condition persisted for five months. The recurring chills usually led to the diagnosis of malaria and also gave rise to the opinion widely held, particularly by French writers, that ulcerative endocarditis could be caused by this disease. The cases to which I wish to call attention in this communication are of this chronic character, not marked specially by chills, but by a protracted fever, often not very high but from four to twelve months' duration. At the time of the delivery of the Goulstonian Lectures I had not seen a case of this type. In the past twenty years I have seen ten cases of this form, two of which I have already reported (*Practitioner*, 1893). I have put them together in tabular form to indicate their main features.

[1] Read at the Association of Physicians of Great Britain and Ireland, Edinburgh, June 12, 1908.

[Q. J. M., Jan. 1909.]

SUMMARY OF TEN CASES OF CHRONIC INFECTIOUS ENDOCARDITIS.

| No. | NAME. | AGE. | DATE. | FORMER RHEUMATIC FEVER. | OLD VALVE LESION. | EARLY SYMPTOMS. | TYPE OF FEVER. | SKIN SYMPTOMS. | EMBOLISM. | HEART LESIONS. | DURATION. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | J. M. | 28 | July, 1888 | Yes | Mitral | Fever | Remittent and intermittent | Painful nodular erythema | None | Mitral endocarditis | 13 months |
| 2 | T. B. | 43 | March, 1892 | No | Mitral | Chills and fever | Remittent | Purpura | None | Mitral endocarditis | 10 months |
| 3 | Florence D. | 21 | March, 1899 | Yes | Mitral | Chills and fever | Remittent | Painful nodular erythema | Brain | No p.m. | 7 months + |
| 4 | Mary B. | 19 | June, 1890 | Yes | Mitral | Chills and fever | Remittent | Painful nodular erythema | Brain | No p.m. | 5 months + |
| 5 | R. B. | 53 | May, 1902 | No | Aortic | Chills and fever | Remittent with chills | — | None | No p.m. | 4 months + |
| 6 | Dr. B. T. | 33 | Sept., 1902 | No | Aortic | Arthritis, chills, fever | Intermittent and remittent | Painful nodular erythema | None | No p.m. | 8 months |
| 7 | Dr. R. T. | 53 | Feb., 1903 | Yes | Mitral | Fever and sweats | Remittent | Painful nodular erythema | Retina, spleen, kidney | Mitral, aortic, and tricuspid endocarditis | 8 months + |
| 8 | R. W. | 36 | Nov., 1906 | Yes | Mitral | Chills and anaemia | Remittent | Purpura | None | No p.m. | 6 months |
| 9 | Dr. C. | 52 | May, 1907 | No | Mitral | Fever | Remittent | Painful nodular erythema | Brain | No p.m. | 7 months |
| 10 | Alice A. | 20 | Jan., 1908 | Yes | Mitral | Fever | Remittent | Painful nodular erythema | None | No p.m. | 7 months |

It has long been recognized that malignant endocarditis is really an acute septicaemia with localization on the endocardium, but the symptoms are not necessarily due to the local lesion. The clinical picture is a septicaemia sometimes of a typhoid type, sometimes like a pyaemia—then again with predominant meningeal symptoms, occasionally with pronounced cardiac features. The pneumococcic, the gonorrheal, and the streptococcic forms present, as a rule, a picture in which the heart-symptoms are in the background. Cases of infection with these organisms may run an identical course without any endocarditis. On the other hand, there is a large group of cases in which the endocarditis plays a more important rôle and the vegetations and ulcerations appear to be directly responsible for the fever and the associated symptoms. As a rule, the valves involved are already the seat of a sclerotic change. The source of the infection is rarely to be determined. Thus, in only one of the series here reported was there an external lesion. The patients in this series were all adults, five women and five men. In six there was a past history of rheumatic fever; eight had old mitral lesions, two aortic, well compensated, and not giving any trouble at the time of the onset of the symptoms. It was not always possible to get a definite history of how the attacks began. In five of the cases there were chills and fever, mistaken for malaria. Cough and loss of weight in some cases suggested tuberculosis. The slight fever without any localizing symptoms may raise the suspicion of typhoid fever. In my series these have been the three diseases the diagnosis of which has been suggested. Once established the fever becomes the dominant, and for months may be the only, symptom. This is the most striking peculiarity of the cases. Week after week, month after month, the daily rise of one and a half or two degrees may be the only indication there is of an existing mischief. In Case I, in which the fever lasted for thirteen months, the patient's sister, a trained nurse, had decorated the room with yards of the temperature charts; fever with an occasional sweat were the only symptoms. The appetite remained good and she lost very little in weight. There were no embolic features and from month to month there were few, if any, changes in the cardiac condition. In this very protracted form chills are not nearly so common as in the more acute cases, nor is the fever so high, not often reaching above 102·5° or 103°. It is of a remittent type, not falling to normal at any period of the day. With the occurrence of a chill the temperature may rise to 104° or 105°, but in none of the cases was there the type of fever in which the paroxysms recur with great regularity—quotidian or tertian, as we see so often in the acute forms of ulcerative endocarditis. Another peculiarity is the occurrence of periods of apyrexia, usually towards the end, but in one or two of the cases there were afebrile interludes which gave deceptive promise of recovery. It is well recognized now that fever is not an invariable accompaniment of endocarditis. Following pneumonia there may be for months a slight toxaemia with little or no fever in connexion with a patch of endocarditis.

The cardiac features in this group are usually well marked, but as a rule

there are no symptoms. The patients complain neither of palpitation nor of pain. There is no dyspnoea except towards the close, and in no case did dropsy occur. In eight of the ten cases there were the well-marked physical signs of a mitral lesion and the associated slight enlargement of the heart. In only six cases was there marked hypertrophy and dilatation. In two of the cases there was aortic insufficiency. One of the most striking circumstances is the very slight change in the character of the heart murmur in spite of the fact of most extensive vegetations and alterations in the valves. Thus in the case of Dr. R. T., with the condition of whose heart I had been familiar for fourteen years, the comparison between my first examination in 1889 and that in 1893 showed very little change beyond the slightly greater dislocation outwards of the apex beat. In several of the cases the absence of any change in the character of the heart murmur and the remarkably quiet, negative state of the organ were urged strongly against the existence of endocarditis. It is rather remarkable, considering the anatomical changes, that so little alteration may occur in the physical signs. In Case VI, Dr. B. T., the murmur of aortic insufficiency became more intense towards the close, but in no instance was there the development under observation of alterations in the physical signs such as are sometimes seen in acute ulcerative endocarditis.

Embolism, to cause symptoms, occurred in four cases of the series—in Cases III, IV, and IX in the brain with haemiplegia, Case VIII in the retinal arteries and in the spleen and kidneys. This is in striking contrast to the frequency of this complication in the more acute types of endocarditis.

One of the most interesting features of the disease and one to which very little attention has been paid is the occurrence of ephemeral spots of a painful nodular erythema, chiefly in the skin of the hands and feet, the *nodosités cutanées éphémères* of the French. My attention was first called to these in the patient of Dr. Mullen of Hamilton, whose description is admirable: 'The spots came out at intervals as small swollen areas, some the size of a pea, others a centimetre and a half in diameter, raised, red, with a whitish point in the centre. I have known them to pass away in a few hours, but more commonly they last for a day, or even longer. The commonest situation is near the tip of the finger, which may be slightly swollen.' Spots of this character occurred in seven of the cases and in three at least they were of importance in determining the diagnosis. Thus in the case of Dr. Carroll, the well-known American Army Surgeon, the collaborator with Dr. Reid in the brilliant work upon yellow fever, the presence of these spots appeared to me to clinch the diagnosis. They are not beneath but in the skin and they are not unlike an ordinary wheal of urticaria. The pads of the fingers and toes, the thenar and hyperthenar eminences, the sides of the fingers, and the skin of the lower part of the arm are the most common localities. In one case they were present in the skin of the flank. I have never seen them haemorrhagic, but always erythematous, sometimes of a very vivid pink hue, with a slightly opaque centre.

The diagnosis in this group of cases may offer great difficulties. For weeks,

indeed for several months, there may be only fever, and unless there have been special features pointing to the heart, such as the development of a diastolic murmur or the great intensification of a mitral bruit, it may be impossible to settle the diagnosis. There are, indeed, cases in which from beginning to close no heart murmur has been present. By far the most suggestive features are: (1) a knowledge of the existence of an old valve lesion. This was present in every one of my series. (2) The occurrence of embolic features, sudden swelling of the spleen, with friction in the left flank, sudden attack of haematuria, embolism of the retinal arteries, hemiplegia or the blocking of a vessel in one of the limbs. (3) The onset of special skin symptoms, purpura, and more particularly the painful erythematous nodules to which I have referred. Present in seven of the ten cases, these are of definite diagnostic import. They are in all probability caused by minute emboli. (4) The progressive cardiac changes, the gradual increase in the dilatation of the heart, the marked change in the character of a mitral murmur, the onset of a loud rasping tricuspid murmur, or the development under observation of an aortic diastolic bruit.

With carefully made blood-cultures one should now be able to determine the presence of the septicaemia. This was easily done in three of my more recent cases. An onset with chills and fever and slight swelling of the spleen almost always leads to the diagnosis of malaria, more particularly in regions in which this disease prevails, but in not one of my cases was there any difficulty in excluding this by careful microscopical examination of the blood. It was not always possible to convince the physician. With slight cough tuberculosis may be suspected, as happened in two or three cases of my series. For many weeks the patient may present nothing but a pyrexia, of doubtful origin, or a cryptogenetic septicaemia, and as he may look very well and may feel very well, and there are no special symptoms, and with a heart-condition that may have remained unchanged for years, it is not easy to reach a positive diagnosis. The blood-cultures and the presence of the painful erythematous nodules and the occurrence of embolism furnish the most important aids.

The anatomical condition in these cases is quite unlike that of the ordinary ulcerative endocarditis. In the three specimens I have had an opportunity of studying there was no actual ulceration, but large proliferative vegetations, firm and hard, greyish yellow in colour, projected from the endocardium of the valves like large condylomata, encrusting the chordae tendinae and extending to the endocardium of the auricle. The condition is quite unlike the globose vegetations of the pneumococcal and gonorrhoeal endocarditis or the superficial ulcerative erosions of the acute septic cases.

The organisms responsible for this condition have been carefully studied. In my series cultures were made in six cases. In three they were negative. In two streptococci were present, in one a staphylococcus. While, as a rule, this condition is much more commonly caused by the streptococcus other organisms may be present. Thus Fraenkel has reported one instance of a pneumococcus endocarditis persisting for nearly six months (*Deutsche med. Woch.*, 1900). Of

sixteen cases of this chronic form, the clinical course of which extended from four to eight months, Harbitz (*Deutsche med. Woch.*, 1899) found pneumococci in four, streptococci in nine, and in eight other micro-organisms. Lenhartz (*Deutsche med. Woch.*, 1901), who has reported sixteen cases with a duration of from three to seven months, found staphylococci and streptococci the common organisms, the pneumococcus once and the gonococcus once. In the majority of cases it seems to be a mild streptococcus infection, possibly by a special form. Possibly in some instances there may be a special resistance on the part of the host, but these are points which must be settled by future investigations. These are cases in which the possibility of successful vaccine treatment should be considered. It was tried in two cases of my series, but in both rather late, and in neither did it seem to have special influence. Horder has treated a case of this chronic type with a vaccine prepared from the patient's organism, but without success. The results in the acute forms are discussed by him in the *Practitioner*, May, 1908. Abstracts of the cases are here given.

*Case I.* J. M., aged 28. I saw this patient with Dr. Mullen of Hamilton, Ontario, in 1888, during my occasional visits to that town, on my way to Toronto. A point of special interest is that the sister of the patient, a trained nurse, had kept a very accurate temperature chart from July 17, 1888, to July 7, 1889, nearly twelve months. Sheets of the four-hourly temperature charts, pinned up on the wall of the bedroom, provided a very remarkable picture.

The patient had had good general health, but at twelve years of age had had rheumatic fever. In February, 1888, she got cold and had pain in the chest. Early in the summer she began to feel badly and had attacks of faintness and the fever came on in the afternoon. When she returned to her home in the first week of July the temperature was as high as 104° in the evening, and she was thought to have typhoid fever. The fever persisted and she had profuse sweats. I saw her in the end of September, and though a systolic murmur was present I did not appreciate that the condition was one of endocarditis. I saw her again at Christmas time, when she seemed very much the same, except that she had been having severe rigors followed by very high fever and profuse sweating. This was the first case in which I noticed the remarkable skin lesions. She had a great many crops which were at first thought to be urticaria. Dr. Mullen's description is most characteristic: 'The spots continue to appear at intervals. They are erythematous, some as small as a pea, others a centimetre and a half in diameter with a white point in the centre. They often pass away in a few hours and rarely last longer than the evening of the day on which they appear. They are not numerous. The commonest situation is near the tips of the fingers, which for a short time become swollen.' These spots were seen more or less throughout the illness, less towards the close than at the early part. At this visit at Christmas we made up our minds that the condition was one of endocarditis. The heart murmur had intensified and there were signs of dilatation of the organ. I saw her again in April, 1889, when there was little or no change, except that she was weaker. She died July 7, 1889, more than thirteen months from the onset of the illness. Dr. Mullen very kindly sent me the heart for dissection. The mitral valves were a little thickened; the orifice admitted two fingers. The margins on the auricular side were covered with large vegetations, many of them extending on to the wall of the left auricle. The chordae tendinae were shortened and thickened and encrusted with vegetations. There were signs of old infarcts in the spleen and kidneys.

*Case II.* T. B., aged 43, admitted to the private ward, Johns Hopkins Hospital, March 13, 1892, complaining of weakness and fever. He had had very good health, with the exception of an attack of typhoid fever twenty years previously and chronic malaria when a lad. Early in December, 1901, he began to have loss of appetite, malaise, and fever with enlargement of the spleen. The fever was of an intermittent type, ranging from 102° to 103°. He had occasional sweats. The spleen was enlarged, and very naturally the condition was thought to be malaria. Throughout the winter the temperature persisted and he had cough, and there was a loud systolic murmur detected at the apex. When admitted to hospital the examination was everywhere negative, except in the heart, the impulse of which was in the sixth interspace, three centimetres outside the nipple line. There was a loud systolic murmur of a musical quality heard as far as the angle of the scapula. The sounds at the aortic cartilage were clear. There was no anaemia. The patient was under observation from March 15 to May 10. The temperature rose daily to between 102° and 103°; about four or five o'clock in the afternoon he sweated. He gained slightly in weight. He complained a little of pain on the left side in the splenic region. Throughout May and June the temperature range was from 97° to 103°. In July the fever was less marked. There were several days when the temperature was almost normal. Early in July for the first time the petechiae appeared. At intervals there were very profuse sweats. Throughout August and September there were groups of days in which the temperature was normal or subnormal, sometimes as low as 95°. He died September 16, about ten months from the onset of his illness. The autopsy by Dr. Block showed an extensive mitral disease. The ventricular surfaces of the valves were studded with enormous masses of vegetation. The chordae tendinae were thickened and encrusted with firm yellow outgrowths. The aortic valves and those of the right side were normal. The spleen and kidney showed infarcts.

*Case III.* Florence M. D., aged 21, seen March 16, 1899. The patient was well and strong as a girl; at seventeen she had severe anaemia. Through the summer she was very well, but tired easily on exertion. In October she began to have feelings of chilliness and irregular fever, and sometimes the joints were a little stiff and sore, but never red. The doctor thought she had slight rheumatic trouble and gave her salicylates, but she never got perfectly well and grew pale and nervous. She had a little cough and it was suggested that she might have tuberculosis. Early in February she had a severe chill. Subsequently she had slight ones at intervals, following which the temperature would rise to 103°. It was then discovered for the first time that she had heart trouble. As she had a cough as well, it was decided to send her South and she was brought to see me on the way through Baltimore.

She was a tall, well-nourished girl, looking a little pale. I was surprised to find the temperature above 103°. The pulse was rapid. The heart's action was violent, the apex beat in the fifth space outside the nipple line. There was a very intense apical systolic murmur, transmitted loudly to the back and also heard in the left sternal margin. There was a soft bruit at the aortic cartilage. There was no swelling of the joints, but on the radial side of the first phalanx of the right index finger were three raised red spots, each about a centimetre in diameter and very tender. They appeared that day, and she stated that they came at various places on her hands and feet and lasted two or three days. The patient was so ill that they were not able to proceed on their journey, and I saw her at intervals for the next six weeks. Symptoms of severe endocarditis increased. Early in April she had left hemiplegia and the spleen enlarged. Numerous crops of the painful spots of the skin came out, four or five at a time, usually about the hands and feet, occasionally in the forearms and legs. She could tell at once when a fresh one started because of a peculiar hot and tingling

sensation. Then it grew red, became swollen and very tender. After lasting from twenty-four to thirty-six hours they gradually faded. They were not specially connected with the tendons. They were in the skin and perhaps a larger number occurred in the palmar surfaces of the hands, particularly about the pads of the fingers. She died April 25, between seven and eight months from the onset of the illness. There was no post mortem.

*Case IV.* Mary B., aged 19, seen with Dr. J. K. Mitchell of Philadelphia, June 16, 1890. The patient had had rheumatic fever as a child but had got fairly well and strong. Her illness began with chills and fever which were thought to be malarial, but no parasites could be found in her blood. When I saw her there were signs of an old mitral lesion—apex beat outside the nipple, impulse forceable, and a loud systolic murmur propagated to the back. The spleen was enlarged. The temperature ranged from 102° to 103° and she had profuse sweats. Crops of painful spots appeared from time to time upon the hands and feet, and a few on the skin of the flanks. This was the second case in which I had seen them. They were red, raised, from 3 to 5 mm. in diameter, and often very painful. The fever in this case lasted about seven months. Towards the end embolic symptoms occurred, with hemiplegia.

*Case V.* July 16, 1902, I saw with Dr. Samuel Ward of Albany, Mr. B., of Cincinnati. I had seen Mr. B. about for several days and noticed that he was not looking very well, but was surprised to find on examining him that he had an old heart lesion, well-marked aortic insufficiency, a loud aortic systolic murmur, and a rough murmur of mitral regurgitation. The patient stated that he had been having malarial fever since the end of May. He had been subject to the disease since 1879. In 1884 he had typhoid fever. He had had attacks of arthritis which were called gout, in one of which in 1898 he had some affection of the heart. The attack at the end of May did not yield to the usual remedies of quinine and Warburg's tincture, and early in June he had a severe chill followed by fever and sweats. He had been up and about, but he had had fever ever since, the temperature occasionally rising to 103°.

From the outset I had no doubt of the nature of the trouble, and had no belief in the malarial theory of the fever, though he came from a malarial district and he had had attacks. Under these circumstances it is always possible to have malarial complications, but there were no crescents in the blood and no pigmented leucocytes. Dr. Ward ascertained that in the second week of April he had bruised his foot on one side, which became red and inflamed, and hot poultices had to be applied. He was in bed for four days. It is quite possible that this may have been a local focus of infection. I saw the patient at intervals with Dr. Ward through August. He had three severe chills. The temperature became more irregular and reached a higher point. He was removed to his home at Cincinnati under the care of Dr. R. W. Stewart. A pure culture of staphylococcus aureus was obtained from the blood. There were no embolic features. He died September 16, 1902, about four months from the onset of the fever.

*Case VI.* Dr. B. T., aged 33, seen September 25, 1902. Early in May while hard at work he began to have fever. As he had been to the eastern shore of Maryland, it was thought to be malaria. Once or twice a week his temperature would rise to 101° or 102°, sometimes with a chill. He lost in weight, but was able to continue work, and in July while away for a holiday he seemed better, though he still had occasional attacks of fever and sweats. For the previous six weeks he had had daily temperature from 100° to 101° and had sweated at night. Occasionally he would feel very cold and at night when getting into bed the teeth would chatter. He had consulted one or two professional

friends who thought he possibly had chronic malaria, and pulmonary tuberculosis was suggested. He had become a little thinner and paler.

He had been a remarkably healthy man with a very good family history. He never had had rheumatic fever or chorea. He had not had gonorrhoea. On close questioning he stated that in April or May, he forgot which, he had a little swelling and tenderness in some of the joints, but it was quite trifling. In 1890 in an examination for Life Insurance Dr. Chew found aortic insufficiency, but he had never had the slightest cardiac inconvenience.

The patient was a very well-built, well-nourished man, looking a little pale. The right wrist-joint was a little tender on pressure, there were no subcutaneous fibroid nodules. There was a well-marked collapsing pulse. The apex beat was outside the nipple line, not forcible. There was a little diffuse pulsation to right of sternum and second interspace. At the apex the heart-sounds were flapping and clear. At the second right intercostal space there was a short, rough systolic, and a well-marked diastolic murmur of slightly wiry quality was heard down the sternum. The spleen was not enlarged. The patellar tendons on either side were tender on pressure. He assured me that the heart features were very much like those which Dr. Chew had noted in 1900, and I felt convinced that the case was one of endocarditis. Throughout October he became worse and was confined to bed. On November 26, when I saw him, he had changed remarkably. He was very pale. Visible pulsation was seen everywhere in the smaller vessels. The spleen was enlarged. The heart had become more dilated, but there was very little change in the murmurs, except that there was now a loud apical systolic. He had had several very painful spots about his fingers and toes, lasting for a day or two. The blood-cultures were negative. I saw him again on December 8, and he was much worse. His feet were oedematous, with petechial spots here and there. He died in January, about eight months from the onset of the fever.

*Case VII.* Dr. R. H. T. In 1889 and again in 1890 I was consulted by Dr. T. for an old mitral lesion which was associated with slight enlargement of the left ventricle. As a boy he had had a mild attack of rheumatic fever. For the next ten or twelve years I saw Dr. T. at intervals and never found any special change in his heart. He was a man who lived a very active life and was able to do a great deal of work, though with limitations. During the year 1903 he was not very well and throughout February he had an irregular fever, never very high, not often reaching 102°. He felt very well and he had no chills. From early in March until his death, October 3 (eight months), he was confined to bed and was under the care of Dr. H. B. Thomas, to whom I am indebted for the copy of the temperature chart. I saw him at intervals. Briefly summarized, the main features were, first, fever, which rarely rose above 102°. After June it became a little higher and a little more irregular and sometimes reached 103°. In August and September it was lower, and after September 17 until his death it was normal. There were no chills. He had occasional sweats.

The condition of the heart was very interesting. In June and July when I saw him the pulse was good, heart's action regular, and there was very little change in the mitral murmur, which presented practically the same characteristics with which I had been familiar since 1889. He had no cardiac distress, as a rule, but just before he was moved in the summer there were two attacks of what were supposed to be angina.

The only embolic features were two attacks in the vessels of the retina in July. He had no painful spots on the skin, but he had painful fingers. On one of my visits he had a well-marked, localized red spot about three millimetres in extent on the pad of one finger. He died suddenly October 3, after an illness of more than eight months. The post mortem, by Dr. MacCallum, gave the

following: vegetative and ulcerative endocarditis affecting tricuspid, mitral, and aortic valves and wall of left auricle; rupture of chordae tendinae and encrustation with vegetations; embolic occlusion of anterior coronary artery at orifice; embolic necrosis of myocardium, cardiac hypertrophy and dilatation; infarctions of various ages in the spleen and kidney; focal haemorrhages in the intestines; acute splenic tumour; the vegetations everywhere were firm, yellowish white, and from the mitral orifice a great mass projected into the auricle and there were large irregular masses on the aortic valves. The cultures showed a streptococcus.

*Case VIII.* In November, 1906, I saw with Dr. Fuller England in Winchester Mr. W., aged 36. He had been under the doctor's care many years previously for acute rheumatism which had left his heart damaged. There was a loud mitral systolic, but there was perfect compensation. Through the summer of 1906 he was not very well and complained of shortness of breath, and in July had frequent attacks of shivering. He began to have inability to rest comfortably at night in the recumbent posture. He lost in weight and became anaemic. He had also slight fever. When I saw him he had been for some weeks in a nursing home. His temperature had ranged from 100° to 101·5°. It was very frequently subnormal in the morning. He had profuse sweats. There was some little doubt at first in the diagnosis, as he had tenderness in the region of the spleen and a dilated stomach. There was a history of tuberculosis in his family.

The patient was very pale and looked thin and ill. There were the signs of old mitral disease with moderate hypertrophy of the heart, a loud thrill and a very intense apical systolic murmur. There was slight infiltration of the bases of both lungs. The spleen was enlarged, but at the time of my visit there were no embolic features. Cultures were made from the blood and a streptococcus was obtained. Numerous injections of a polyvalent serum were made which seem to have reduced the fever slightly, and it caused a good deal of drowsiness. For a month before his death there were numerous embolic patches on the skin with purpura. The patient lingered until December 8. The temperature chart is very interesting. The fever was never high, not once passing above 102°. Towards the end, for the month before his death, it was rarely above 100°. Anti-streptococcic serum seemed to have reduced the fever very much.

The entire duration was about six months. A point of interest in the diagnosis is that the case began with symptoms of shivering, sometimes a definite chill, and as he had an enlarged spleen it was suggested at first he had malaria. Then the distension of his stomach and indefinite swelling in the left side of the abdomen aroused the suspicion of cancer. Later, a slight cough, the fever, the infiltration of both bases, and the man's general appearance suggested tuberculosis.

*Case IX.* May 8, 1907. I saw in Washington, with Dr. Hardin, Dr. J. C., aged 52, well known in connexion with his work on yellow fever. He had had the ordinary diseases of childhood, typhoid fever in 1886, yellow fever in 1900. He passed the physical examination for the Army in 1902. For several years he had known that there was a lesion of the mitral valve which was detected in a Life Insurance examination. On the evening of February 18 he felt chilly and did not rest well. The next forty-eight hours he was depressed, had cough, and his temperature rose to 102·8°. From that time until the day I saw him he had had regular fever, rarely reaching above 102·5°. He had sweats, more particularly in the early morning hours. As he had a little cough and had lost in weight, it was very natural that tuberculosis was suspected. Dr. Ruffin, Dr. Thayer, Dr. Barker, and others saw him and it did

not seem possible to arrive at a satisfactory diagnosis, as the physical signs were so slight and there was nothing but the fever.

He looked very well, not specially changed in appearance since I had last seen him. There was no alteration in the skin. I made a careful examination, which was negative everywhere except the heart. There was slight enlargement of the left ventricle and there was an apical systolic murmur propagated beyond the mid axilla, and there was a loud pulmonic second sound. His physicians could not determine that there had been any special change in the condition of the heart or in the murmur. He complained of very peculiar spots on his skin, chiefly about the arms and fingers, sometimes on the toes and feet. They came in crops, lasting from one to five days. Each spot was raised, a little red, and felt like a localized infiltration of the skin. They were chiefly on the fingers and on the palms of the hands, sometimes along the forearm. When I saw him, two or three were just disappearing. I did not think that there was any question as to the nature of the case. The mitral lesion, the irregular, persistent fever, and the spots suggested strongly the chronic septic endocarditis. Throughout the summer the condition remained practically the same. The fever persisted, the oscillations of temperature a little greater; he continued to have occasional eruptions of the spots on his fingers, the crops lasting for two or three days. There were no other signs, no audible change in the heart lesion. On September 15, 1907, he suddenly lost power of speech and got right hemiplegia, and he died in fourteen hours. About fifteen blood cultures were taken, all negative. The duration of this case was exactly seven months.

*Case X.* January 13, 1908. I saw, with Dr. Ward and Dr. Powel of Southampton, Alice A., aged 20. Five years previously she had rheumatic fever, a severe attack with cardiac complications and very slow recovery. Twelve years previously she had a very deep-seated gland removed from the right side of the neck. It was probably tuberculous. The hypoglossal nerve was involved and it had left her with atrophy of one side of the tongue. The previous winter she 'came out' and had a very busy season. She danced and skated and seemed very well. In February she had tonsilitis, not a very severe attack, but she had not been quite well since. She was pale and was often weak and nervous. This was attributed by her mother and the doctor to a love affair which had worried her. Some weeks later she began to have a slight fever and the doctor at first suspected that she might have tuberculosis, but the lungs were negative. Then through the summer she was not well, and on and off had febrile attacks, which increased in September. In October it was thought best that she and her mother should go abroad and spend the winter. On the steamer she got very much worse and it was found she had a temperature of 103°. She landed about the end of October and had been in a nursing home ever since. The symptoms had been—(1) Fever, which had ranged from 100° to 102°, only within the past week had it crossed the 103° limit; (2) she had had at times drenching sweats so that the bed-clothes had had to be changed; (3) she had lately had great irritability of the stomach, constant nausea; (4) on several occasions on the tips of the fingers there had appeared red spots, exceedingly tender swellings, looking very angry and almost, as Dr. Ward said, as though they would suppurate and then they gradually subsided.

There was no pain and no distress about the heart; the urine was clear; the sputum had been examined, as, of course, tuberculosis was at first suspected. She had wasted a good deal. I found a girl looking a little pale, but not so thin in the face as in the body. There was marked general anaemia of the skin, much more so than the face would indicate. The pulse was small, about 110. There were no petechiae. The heart was moderately enlarged, the impulse forcible, wavy, and extended from the second interspace to the fifth, an inch

outside nipple line. There was a very intense mitral systolic heard everywhere over the heart, loudly up the left sternal margin and transmitted to the spine. Though rough and harsh, Dr. Ward did not think it had specially changed in character. The second sound was everywhere clear.

Within three or four days there had been a slight infiltration at the lower lobe of the left lung. The percussion note was impaired and the breath sounds tubular. The apices and other parts were clear. The abdomen was a little swollen, nowhere tender, slightly tumid in the epigastric region; the liver was not enlarged, the edge of the spleen only just palpable. She died about seven months from the onset of the fever. It is quite possible that the onset of the attack may have been in February, when she had tonsilitis, in which case the duration was over a year.

CRITICAL REVIEW

# THE PATHOLOGY OF URAEMIA

By FREDERICK GOLLA

In no branch of pathology has research made so little progress during the last fifty years as in the understanding of the pathogenesis of the symptom complex that we know as uraemia. This failure is the more surprising in that we have strong grounds for assuming that, unlike the complex toxaemias accompanying bacterial infection, we are probably confronted here by a problem the elucidation of which, from a chemical point of view, is well within the compass of modern methods of research. It would be a retrograde step were the facile explanation of this failure to be adopted that uraemia is no pathological unity, but rather a terminal condition, in which the various physiological systems of the organism manifest, some more and some less, a general lack of equilibrium and a disorientation of function due to the accumulated influence of the retained products of katabolism. It is no part of this paper to consider the clinical syndrome of uraemia. The clinical aspect has been reviewed in a masterly manner in Ascoli's (1) splendid monograph, without frequent reference to which no consideration of the subject can be complete. To any one who sufficiently studies the clinical literature, and dissects away the irrelevant from what may be called the essential features of the syndrome, one fact presents itself as beyond all doubt, and that is the preponderance of disturbances of the central nervous system over all other symptoms and the remarkable similarity of these nervous manifestations. In fact, uraemia may be called a specific toxic disease of the central nervous system, which may or may not be complicated by a primary affection of other physiological systems, and, as a disease, it manifests a degree of clinical unity in the predominance of certain irritative and paralytic symptoms, which, by their constancy and definition, must drive us again to search for a specific causation.

It would be unwise to push this line of argument too far. A causal unity need not be sought for the various visceral and cutaneous manifestations of uraemia but neither need they be considered as essential parts of the uraemic syndrome.

It was an early recognition of the essentially nervous origin of uraemia that drove some of the first workers at the subject to the formulation of mechanical theories of uraemia which we shall now consider briefly.

*Physical Theories.* Owen Rees (2) in 1850 first drew attention to hydraemia of the blood occurring in uraemia, and suggested that oedema of the central nervous system occurred as a consequence of the uraemia and was the cause of the con-

vulsive and comatose symptoms. Traube (3) ten years later elaborated this idea. He considered that the left-sided cardiac hypertrophy caused a rise of blood pressure, which was intensified by the condition of hydraemic plethora. If this rise of blood pressure were still further increased, or the osmotic tension of the blood still further lowered, serous fluid transuded into the cerebrum from the veins and capillaries. Since, however, the aortic pressure is greater than that in the veins and capillaries, these latter are compressed, and to the cerebral oedema is added cerebral anaemia. Coma he considered to be a consequence of the oedema and anaemia of the cerebrum, and the motor discharges as due to the same process taking place in the mid-brain, the one or other symptom being accentuated according to whether the lesion were chiefly localized in the cerebral hemispheres or the mid-brain. This theory is now only of historical interest, and was doomed to failure, first, because it started from the untenable position that increased arterial blood pressure may cause cerebral oedema, and next because cases are not wanting in which uraemia takes place in the presence of lowered arterial tension. The experimental work of Munk (4) in support of Traube's theory involves operative procedures which leave no parallelism possible between the condition of his animals and that of the uraemic patient. The work of Traube was of some interest as a means of drawing attention to the great frequency with which cerebral oedema occurs in post-mortem examinations of uraemic cases, and Bartels was probably wrong in attributing this to the result of fits, from which the patient may have suffered. Cerebral oedema is by no means universal in uraemia, nor is it so extreme as may sometimes be found in other conditions. Cerebral oedema may possibly be invoked to account for the strictly localized palsies of the uraemic and the frequent occurrence of amaurosis, though it must be noted that in cases of cerebral tumour, in which symptoms distant in origin from the seat of the lesion have been ascribed by Collier (5) and others to oedema and pressure, the nerves most commonly affected are the sixth pair, whereas a palsy of the external rectus is a relatively rare event in uraemia.

The older view that ascribed uraemia to meningeal inflammation is now only of historical interest.

Attempts have been made to explain uraemic symptoms by local cerebral vaso-constriction. It is obvious that such an explanation does not permit of post-mortem verification, and it may be doubted whether the phenomena of kryaesthesia and formication, on which Ascoli lays such stress, are other than paraesthesiae accompanying, as they so frequently do, lesions of the cerebral cortex. It is doubtful, moreover, whether provision exists for local vaso-motor action in the cerebral vessels.

Another mechanical theory (6) that has little to support it is one that rests upon the supposed increase in the viscosity of uraemic blood offering such an impediment to tissue circulation that an accumulation of waste products results in the tissue cells (Ewald).

*Chemical Theories.* We may consider the chemical theories of uraemia as

being capable of classification under two heads—first, those theories attempting to explain the uraemic syndrome as being due to the toxic action of some constituent of normal excretion which has been retained owing to the deficient eliminating power of the kidneys, and secondly, the theories which try to account for uraemia by assuming some abnormal metabolic process consequent on the deficient elimination of waste products and resulting in the intoxication of the organism by some abnormal products of metabolism or of interaction between the retained substances. Lastly to be considered are those views according to which uraemia is due to an intoxication resulting from the action of bodies formed by the autolysis of renal tissue.

In considering the first group, or theories of intoxication by the retention of normal excretory products, I do not propose to follow any strictly chronological order. It will save needless repetition if we first examine the basis on which any theory of urinary retention as a cause of uraemia must rest, and any objection urged against the occurrence of uraemic symptoms due to urinary retention must equally apply to arguments founded on the toxic properties of constituents of the retained urine.

First then we must inquire as to the degree in which symptoms due to retention of urine resemble those of uraemia. There is no necessity here to insist on the results obtained by experimental methods on animals. Numerous experiments have shown that in the dog and rabbit suppression of the urinary excretion by ligature of the ureters leads to death in about three days, and that this period is rarely exceeded (8). It is obviously of far greater importance to examine the observations of clinical cases in which sudden occlusion of the ureters has occurred in men with healthy or relatively slightly impaired kidneys. By studying the symptomatology in man we can definitely assure ourselves of the relationship of uraemia and anuria to one another.

To examine critically in detail the large amount of clinical material that has been reported with reference to anuria would be beyond the scope of this paper. Ascoli has dealt with the phenomena of anuria in an extensive fashion and comes to the following conclusion:—'Severe urinaemia in man is chiefly manifested by the occurrence of bodily weakness and languor that is often first manifested before the occurrence of any other symptoms, but generally leads on to progressive mental weakness and exhaustion, often terminating with great suddenness. The greater part of the most prominent symptoms of uraemia are, however, lacking, especially the severe and acute mental disturbances, the sudden amaurosis and epileptic phenomena in general. It is true that epileptic discharges are occasionally noted, but not more frequently than in any other severe disease. Only in occasional cases do the symptoms of suppression of urine resemble uraemia.' Thus far it would seem that Ascoli (9) would have the support of the majority of clinical observers, but he appears to go too far in the conclusions that he draws. No one can have failed to note that in a number of cases a certain similarity underlies the two symptom complexes, and it is questionable how far we are justified in comparing the rapid effect of occlusion

of the ureters with the slow intoxication of uraemia. In addition the problem is not quite so simple as to be stated in these terms. With Blum (10) we may distinguish *uraemia*, i. e. the effects due to toxic products of metabolism before their passage through the kidney, and *urotoxaemia*, the absorption of urinary toxic bodies after their passage through the kidney. Now any condition of urinary obstruction must be a compound of these two forms of intoxication. It is true that shortly after the onset of obstruction the flow of urine is brought to a standstill, either by mechanical pressure or by the mechanism of the uretero-renal reflex which has attracted the attention of many observers (11); but, in addition, absorption of the secreted urine from the kidney tubules, possibly in the pelvis, has to be reckoned with.

It would appear that we must exercise extreme caution in any comparison between the symptomatology of uraemia and urinaemia, that is, of renal obstruction, as judged from a purely clinical standpoint.

Rommelaere (12) as early as 1867 pointed out in the course of his extensive critical and experimental work, that it is fallacious to endeavour to trace the cause of uraemia to any one or other of the urinary constituents, and that the toxicity of the urine must be regarded as the sum of the toxicity of its various components.

It is now necessary to consider whether the urine as a whole contains bodies capable of giving rise to toxic symptoms. An answer to this question has been supplied by the work of Bouchard (13), and it cannot be said that much has been added to our knowledge of the subject since he wrote his well-known work on auto-intoxications. Bouchard claimed to have shown that in the twenty-four hours' urine of a healthy man the toxicity reckoned out per kilo of body-weight remains almost constant. This he terms his coefficient of toxicity. The toxicity was determined by the injection of a specimen from the twenty-four hours' urine into rabbits; he attempts to assign a definite toxic value to the several constituents of the urine, and since, as soon became manifest, the sum of the toxicity coefficients of the known constituents of the urine is in no way equivalent to the high toxic efficiency of pure urine, he attempted with success to separate toxic bodies other than these from the urine. From charcoal which had been shaken up with urine he obtained, on extraction with water, a body which on injection gave rise to convulsions. Another toxic body causing salivation was obtained from an alcoholic extract of the residue of urine evaporated to dryness. He found that in cases of nephritis the toxicity of the urine was diminished, and that this was especially so in uraemia. Hence he concluded that in this condition toxic products of metabolism and of absorption from the intestine were retained in the body owing to renal inefficiency. Although his work is everywhere marked by care and scientific acumen the methods at his disposal present so many fallacies that constancy of results is unobtainable even by use of the most rigid technique. It is possible that some idea of the relative toxicity of the urine may be afforded by his methods in extreme cases. Even in uraemia observers have failed frequently to demon-

strate any diminution in the toxicity of the urine, and his method cannot be said to have been of any service in either the diagnosis or prognosis of renal cases.

Round the subject of urinary auto-intoxication a mass of literature (14) has grown, but the net result is to leave the reader convinced that while the toxicity of normal urine is proven, and pathological variations in its toxicity are probable, there is no method at present at our disposal that allows us to draw any helpful conclusions as to the extent of these variations. The question of the variations in urinary toxicity must be settled by delicate chemical methods rather than by such gross experiments as those of Bouchard and his school.

So far then neither of the two fundamental questions that we have just considered have been answered in a satisfactory fashion. It cannot be said that the relationship of the symptoms of urinary obstruction to uraemia absolutely negative the conception that the same form of intoxication may underlie to a certain extent both conditions, though the many points of dissimilarity make this idea highly improbable for the majority of cases of urinaemia. Again, the work of Bouchard and his school has thrown no very definite light on the question of the retention of toxic bodies in the urine. We may now examine briefly the evidence of the relationship of uraemic intoxication to the several constituents of the urine.

The possibility of urea being the toxic agent was naturally the earliest to be considered. The earliest work on the estimation of urea in the blood in uraemia appears to have been that of Babington (15) in 1836. This observer found that in a case of uraemia under the care of Bright there was as much urea in the blood as in the urine! Wilson (16), in 1833, had already suggested that urea was the cause of death in uraemia, and Christison (17), six years later, also wrote on this subject.

The older results obtained after the method of Mörner, in which all the nitrogen precipitable by phosphotungstic acid was reckoned as urea, showed as a rule a more or less pronounced diminution of urea in the urine in cases of nephritis and uraemia, and this was considered to be retained in the blood, giving rise to toxic symptoms. Part of this diminution may undoubtedly be accounted for by the increase of ammonia. Modern methods have, however, shown that not all the nitrogen precipitable by phosphotungstic acid is to be reckoned as urea. Schöndorff and Kruger and Schmidt (18) showed that a large proportion of the phosphotungstic acid filtrate is composed of amido acids, oxyproteic acid, and perhaps other unknown substances.

These bodies, which amount to some 4 to 5 per cent. of the non-precipitable nitrogen, vary more considerably in nephritis than in the normal subject, though spread over a long period the total excretion does not differ from the normal. No direct relation between their percentage values and the gravity of uraemic symptoms could be demonstrated. As to the urea fraction the new methods afford no evidence of its retention in preference to other constituents of the urine in animals, and modern estimations of urea in the blood fail entirely to furnish any support to this idea. The possibility of urea being the toxic agent

in uraemia may finally be dismissed on the strength of the experiments made with it on animals. The net result of the experimental work has been to show that urea is only toxic in quantities far exceeding those that can ever be found in the blood in experimental conditions.

Frerichs (19) developed the theory of uraemic intoxication by retention of urea along new lines in 1851. While recognizing that the symptoms of uraemia could not be directly referred to urea poisoning, he considered that this body was retained in the organism and gradually accumulated in a patient suffering from nephritis. He explained the sudden onset of the acute symptoms by the intervention of a ferment which converted the accumulated urea into ammonium carbamate. He claimed to have proved his theory, first, in that he had observed after injection of urea into the veins of nephrectomized animals the appearance of ammonia in the breath and blood and secretions, and secondly, that he could induce the symptoms of uraemia by intravenous injection of ammonium carbamate. According as to whether the formation of this body proceeds more or less rapidly, the uraemia is of an acute or a chronic nature. Demjanow (20) supported Frerichs' views by showing that the injection of urea and a ferment into nephrectomized dogs produced uraemia rapidly, while neither of these bodies alone had a marked effect, and that during and after such uraemic attacks ammonia could be demonstrated in the carotid blood.

The work of Frerichs marked a new departure in the investigation of the pathology of uraemia, inasmuch as for the first time the cause of the intoxication was sought for, not among the normal constituents of the urine but among bodies formed by the result of pathological metabolism. It is obvious that the views of Frerichs had to stand or fall with the conclusions that could be drawn from the examination of uraemic blood and tissues for ammonia. The work of v. Jaksch and Treitz (21) for a time lent additional authority to the conception of uraemia as being due to ammonia intoxication.

Treitz, however, considered that the conversion of urea to the ammonium compound took place, not as Frerichs conceived, in the blood, but through the destruction of urea in the intestine and occasionally in the bladder. There seems no doubt that such a condition may occur in certain cases of cystitis. Many authors, including Rumpf (22), have shown that ammonia when ingested as food in the shape of ammonium sulphate has a very considerable toxicity. The more recent work has, however, only tended to confirm the destructive criticism of Kruse (23) on Frerichs' views.

Whilst Winterberg found in three patients suffering from uraemic coma a marked increase of ammonia in the blood, the results of Strauss on the blood of non-uraemic cases of parenchymatous nephritis and granular kidney far exceed the values obtained by Winterberg (24). Salaskin (25) was unable to show any increase in the ammonia in the nervous system of a uraemic patient. In the urine ammonia tends to increase with the onset of uraemic conditions. In one case of uraemia v. Noorden (26) found as much as 1·80 grm. of ammonia nitrogen in 9 grammes of total nitrogen. There appears, however, no justification for the

view of Senator (27), founded on the ammonia increase, that uraemia is due to a condition of acidosis. Numerous observations on diabetics and starving men have shown that the ammonia may be enormously increased without any symptom of acidosis (Weintraud, Magnus, Levy, Golla).

Voit, and later Feltz and Ritter (28), brought forward the view that uraemia was due to the retention of potassium salts, and their contention received some support from other observers. Experimental work, however, has shown an entire absence of correspondence between the two symptom complexes, and numerous estimations of potassium in the blood have shown that its increase in uraemia is by no means an invariable event, nor is it as a rule so marked as the propounders of this theory supposed (29).

Jaccoud, in 1881 (30), brought forward a theory propounding creatinaemia as a cause of uraemia, and based his conclusions on the older estimations of creatin in uraemic conditions of the blood made by Schottin, Oppler, and Perls (31). His work received support from Landois (32), who showed that the local application of creatinin to the cerebral cortex caused convulsions and coma. Feltz and Ritter, Bouchard, and Leubuscher (33) have, however, shown that creatin is never present in sufficient quantity in the blood of uraemia to cause toxic symptoms. Creatinin, which is much more powerfully toxic than creatin, is only found in traces in the blood and organs, and only first appears from creatin in the kidneys. Creatinin only occurs in an infinitesimal amount as a free base. It has been shown to be diminished in the urine of cases of nephritis (34). Gautier (35) is quoted by v. Noorden as suggesting that perhaps creatin may be converted in the body of the uraemic into the highly toxic methylguanidin.

Garrod (36), and later v. Jaksch, found that uric acid is increased in the blood in nephritis, and for a time this was regarded as a causal agent of uraemia. Numerous observers have, however, shown that the percentage of uric acid in the blood of uraemia is often surpassed by that of the blood in various diseases, such as pneumonia, gout, and leukaemia, in which there are certainly no symptoms of uraemic nature, and it is hardly necessary to pursue the subject further.

What has been said of creatinaemia holds true of the theories which have been advanced on behalf of all the other extractives. It has been shown that all will give rise to convulsions and coma when locally applied to the cerebral cortex, but there is no proof that any one of them is present in sufficient quantity to account for the symptoms of uraemia. In a little-known piece of work Thudichum advanced the view that uraemic intoxication is due to a retention of pigment substance, basing his idea on observed differences in tint of uraemic serum. Such differences, however, occur in many diseases, and also in normal blood.

Bohne (37) called attention to a suggestive relationship between retention of chlorides and uraemia; but without reviewing the enormous literature that has grown up about the subject of the retention of the chlorides in nephritis, one may cite the work of H. Strauss (38), who showed a far greater percentage

of chlorides in the blood of three cases of nephritis without uraemia than was present in four cases of uraemia.

We may here close our review of the theories attributing uraemia to intoxication from the retained normal products of excretion. We have seen that the work of Bouchard and his school has failed to throw any light on the subject of uraemia, in that they have failed to prove retention of their toxic bodies in uraemia, and that clinical observation tends to show that the symptoms of retention are different from those of uraemia. The claims put forward for each of the constituents of normal urine separately considered have failed to carry conviction to the majority of observers.

The possibility that uraemia may be the expression of the effects of an abnormality of proteid metabolism offers itself as the legitimate alternative to the theories dependent on retention of the normal urinary products. The nitrogen not bound to the proteids of the blood consists, as we have already said, of urea and different nitrogenous bodies, which are usually grouped together under the term suggested by Strauss of 'retention nitrogen'. This name is a misleading one, as v. Noorden (39) has pointed out, inasmuch as in normal blood 1·5 to 2·5 per cent. of the total nitrogen is to be found in this condition and cannot be considered as retained nitrogen.

Filtration nitrogen has been suggested by v. Noorden as a non-committal term. Much might be hoped for from the investigation of the variations in this filtration nitrogen as an index to the possible abnormalities of nitrogen metabolism in the uraemic. A large amount of work has been done on this subject. Taking urea and the filtration nitrogen together, the more modern work only affirms the older results. As pointed out by v. Noorden (40), the net result of the work of Ascoli, Strauss, Botazzi, and Pierallini, of Landau and of v. Jaksch, fully confirms the older work of v. Noorden and Ritter, who showed that there is no relation between the retained nitrogen and the gravity of renal disease. The same may be said of the filtration nitrogen of the tissue fluids which runs parallel to that of the serum. Ascoli has definitely shown that cases of uraemia occur in which, in comparison with those of non-uraemic nephritis, there is no notable increase of the total value of the retained nitrogen. The history of the attempts made to gauge the retention products in the blood by physical methods throws equally little light on the subject. The cryoscopic method allows us to gauge the molecular concentration of such retention products in the blood, though our knowledge as to their absolute value can only be controlled by some knowledge of the constancy or variations of the blood volume. That such variations occur may be considered certain, but any estimation of the blood volume, unless we adopt the very questionable method of Haldane and Lorrain Smith, lies entirely outside our power. The literature on the subject of cryoscopy in nephritic blood has reached very large proportions (41). Nearly normal values for the freezing-point have been found in uraemia by Koryani and Roseman, though, as a rule, the depression is great, often reaching as much as 0·75° C. As Strauss remarks, an increase of $\Delta$ is a concomitant

phenomenon, but not the cause of uraemia. Uraemia is, however, the condition in which the most frequent and highest values of $\Delta$ are found. As we have already remarked, our absence of knowledge of the relative hydraemia or concentration of the blood must make results obtained by this method very difficult, if not impossible of interpretation. The determination of the electro-conductivity of the serum has given no positive information as to uraemia. A certain increase is occasionally observable, and Bickels (42), who has devoted special attention to this subject, finds that such a rise of conductivity cannot be considered a specific attribute of uraemic blood. It would seem as though the greater part of the molecular concentration in uraemic blood, verified by the method of cryoscopy, were due to an accumulation of non-electrolytes.

Observations on the alkalinity of the blood afford some evidence of the disturbances of the metabolic processes in uraemia. In the absence of any method affording us a clear understanding of what observations on the reaction of the blood as tested by various reagents really means, no very clear deductions can be drawn from such results. The majority of the results recorded were obtained by the method of Loewy, and show a distinct decrease in the alkalinity of uraemic blood (43). We have already pointed out that the increase of ammonia in the urine does not, as Senator thought, justify our considering that acidosis is responsible for the uraemic syndrome, and the occasional occurrence of diacetic acid and acetone in the urine of uraemics is only what might be expected in patients occasionally reduced by vomiting or the maniacal refusal of food to a state of extreme inanition.

The chemical determination of some body formed in the nephritic patient as a result of the abnormal metabolism may afford us a valuable clue. I propose to deal with the probability of trimethylamine being such a body at rather more length than is customary in a review of this nature, inasmuch as most of the work, which was done in the research laboratory of St. George's Hospital, has not previously been published, and hence to be of any use as evidence requires a certain amount of detailed exposition. The peculiar 'urinous smell' of the uraemic patient has been long known to clinicians. It was described by Christison (44) in a case of Bright's disease in 1839. Frerichs, who considered it to be due to the ammonia excreted by the breath, attached considerable importance to this point in the exposition of his theory of ammonium carbamate poisoning as a cause of uraemia. The proof of the ammoniacal origin of this smell was, however, by no means well established. Kaup and Jürgenson (45) failed to prove the presence of ammonia in a case in which the urinous smell was strongly marked. Senator noticed that the smell was more intense before the onset of a convulsive attack in uraemia, and was inclined to attribute to it some prognostic importance. He pointed out, moreover, that the smell did not resemble ammonia, but rather trimethylamine. Senator (46), in a paper on auto-intoxication through abnormal disintegration products, demonstrated the presence of trimethylamine in the decomposing urine in a case of cystitis, and

basing his view on the work of Gäthgens (47), who found that trimethylamine was a toxic substance, he considered that the absorption of trimethylamine in this case of cystitis was probably the cause of the toxic symptoms observed. He made, however, no attempt to demonstrate its presence in the blood. Since this paper I have been unable to find any further reference to the subject of trimethylamine in uraemia. Unaware at the time of the observation of Senator, I was impressed by the similarity of the smell of the uraemic breath to that of trimethylamine. It was found to be remarkably constant in all the uraemic cases examined, and most marked in those in which epileptiform attacks were the leading symptom. As an index of the onset of uraemia an exaggeration of the tendon reflexes was recorded and the uraemic odour in two cases became most marked about that time. I find that independently Stevens (48) had drawn attention to the exaggeration of the tendon reflexes about the same time. In three cases of urinaemia, due to ureteral obstruction, I failed to notice the trimethylamine smell, and on questioning colleagues of wider experience, the impression was gained that the urinous smell is always absent in urinaemia. On this point the literature appears to be silent.

Serono and Percival (49) in 1899 communicated a preliminary notice of a method for the determination of trimethylamine in urine based on the Hoffmann process of the precipitation of the fatty amines by neutral ethyl oxalate. By their method they obtained such high values for trimethylamine in the human urine that it appeared that nearly the whole of the basic substance liberated from the urine by weak alkalies, and which has been generally considered to be ammonia, is in reality trimethylamine. Their methods were criticized and the question thoroughly investigated by Filippo di Filippi (50) in 1906, and he worked out an easy method for the estimation of trimethylamine in the urine. This may be briefly detailed as follows:—The twenty-four hours' urine, or as much of it as convenient, is placed in a flask of about three litres capacity containing 10 grm. of KOH in pieces and a few lumps of paraffin. The flask is immediately connected with a condenser leading into a flask which communicates with the external air by means of a Peglioti tube. The Peglioti tube contains glass beads just covered with dilute HCl, and the collecting flask holds about 100 c.c. of hydrochloric acid of 1·19 sp. gr. diluted to a third. The distillation flask is then slowly heated up till distillation begins and then vigorously boiled; the volume is kept approximately constant in the distillation flask by the addition of water through a feeding-cock. After about an hour and a half distillation is terminated, and the contents of the receiving flask and the Peglioti tube are washed out into a large evaporating dish after first assuring oneself that they are acid. The dish content is now evaporated to dryness. The residuum is treated with absolute alcohol and thoroughly stirred. The filtrate from repeated extraction is collected, evaporated to dryness, and the extraction repeated three times. These three extractions are sufficient to get rid of all the amines which are mixed with ammonium chloride. The dry residue of the last extraction is dissolved in a small amount of water and intro-

duced into a flask of about two litres capacity which is joined up with a vertical condenser leading into a flask of about 500 c.c. capacity, which communicates with the external air by a Peglioti tube of about 15 c.c. capacity. On account of the action of bromine on rubber the whole apparatus is of glass, the parts being ground to fit one another. The Peglioti tube and the collecting flask hold about 20 c.c. of hydrochloric acid diluted to a third. Into the distilling-flask 25 c.c. of freshly prepared sodium hypobromite is introduced and the mixture agitated till the evolution of gas ceases. Some of the trimethylamine comes off with the nitrogen and is collected by the HCl in the Peglioti tube. The bromine is now distilled off with strong HCl, and the distillate when bromine ceases to be evolved is collected into a large porcelain evaporating-dish and evaporated to dryness. The distilling-flask is now again coupled up with the receivers, which contain the same amount as before of dilute HCl, and distillation continues till about 300 c.c. have been collected. The distilling fluid is kept at a constant volume. The distillate is washed out and evaporated to dryness, and added to the residuum of the bromine distillate, from which all the bromine has been removed by evaporating with strong acid. The combined distillate represents the yield of trimethylamine hydrochloride, and this may be converted into the platinum salt and estimated by weighing. The whole process takes about two and a half days. The work has been carefully checked by numerous control experiments, for which reference must be made to di Filippi's paper. The results appear to have been satisfactory, and the excessive values of Serono and Percival are to be explained by the presence of the primary and secondary amines which were not taken up by the oxalic ether.

De Filippi was thus able to establish the fact that trimethylamine is a normal constituent of the urine, and can be estimated with a fair degree of accuracy. He found in normal individuals a considerable personal element in the values obtained, which varied from 0·02 grm. per diem of trimethylamine to 0·01 grm. on a mixed diet. He obtained a marked increase of trimethylamine on adding 500 grm. of meat to a carbohydrate diet, and a less marked increase on adding the yolks of ten eggs. The latter result is surprising in view of the probable origin of trimethylamine from a lecithin base.

In the course of last year I endeavoured to determine the trimethylamine variations in the blood and urine of cases of nephritis and uraemia. A series of determinations on four normal people by di Filippi's method gave a urinary excretion for the twenty-four hours of 0·02 grm. trimethylamine as an average result. The same mixed diet was adhered to in all cases, and the highest results were 0·035 and the lowest 0·019 grm. per diem. I found my results a little more uniform than those of di Filippi, and failed to notice the same individual idiosyncrasy. The trimethylamine was estimated by weighing the platinum salt instead of direct titration into acid, as di Filippi appears to have done in his estimations of normal urine. The results obtained from three cases of chronic nephritis corresponded fairly well with those obtained in the normal individual —the mean value being 0·029 and the highest 0·034. I found no trimethylamine

in the faeces of two cases of nephritis. Di Filippi had failed to find it in the faeces of normal individuals.

Adopting a technique not markedly differing from that of di Filippi, I next attempted to find trimethylamine in normal blood. After subjecting several litres of ox blood to this process a little more than 0·4 grm. of a yellow platinum salt was obtained. This salt gave on combustion 0·4 per cent. of hydrogen and 13 per cent. of carbon. The theoretical value for trimethylamine platino-chloride should be 3·79 per cent. of hydrogen and 13·65 per cent. of carbon. Two further supplies of 0·25 and 0·3 grm. of the platinum salt obtained from ox blood gave on heating 0·38 and 0·39 per cent. of platinum, the theoretical value for the platinum in the trimethylamine platino-chloride being 36·92 per cent. These figures, though obtained from very small amounts of the salt, would appear to indicate that the body I obtained was trimethylamine. The salt obtained gave a very distinct characteristic odour of trimethylamine on heating. The method of di Filippi appears to negative the possibilities of the presence of the mono- and diethylamine chlorides. It was next sought to determine the amount of trimethylamine present in human blood free from renal disease. Advantage was taken of venesections performed for therapeutical purposes in eight cases. These were two cases of pneumonia, four of morbus cordis, and two of hemiplegia. The amounts of blood investigated varied between 270 c.c. and 380 c.c. The platinum salts obtained were calculated as trimethylamine, and gave amounts of trimethylamine per cent. which varied between 0·0018 and 0·0011 grm. The amount of platino-chloride crystals obtained were, of course, too small for these measurements to pretend to any great degree of accuracy or for an estimation of the platinum to be performed.

The trimethylamine content of uraemic blood was next investigated. In each of these cases there was a well-marked odour of trimethylamine in the breath.

*Case I.* Uraemic symptoms had succeeded acute nephritis and the patient had been treated at home. For a week before admission to the hospital he had been passing highly-coloured urine in very small amounts, and complained incessantly of headache. Three days before admission amaurosis appeared, and he remained blind up till the time of his death. About the same period he began to suffer from frequent epileptiform fits and was maniacal. The patient was seen for the first time after a series of fits, and was in a comatose state, with the breath smelling strongly of trimethylamine. The respirations were grouped. 300 c.c. of blood were removed. Forty-eight hours after he died. The blood itself smelt strongly of trimethylamine, and the amount of this body obtained as a platinum salt gave 0·018 per cent. of trimethylamine as the percentage in the blood; that is, about ten times the percentage of normal blood. The amount of urine passed in the twenty-four hours succeeding the venesection was twelve ounces, and the total amount of trimethylamine obtained was 0·024 grm. This is considerably above the percentage in the urine of normal people, though the total amount for the twenty-four hours is only slightly above that which I found for an average man taking practically no food. The post mortem showed a condition of acute nephritis.

*Case II.* The patient—a full-grown youth of twenty—had been suffering

from uraemic fits for a week, and was in a state of dementia. He was bled shortly before his death. In this case a strong smell of trimethylamine was noticeable in the breath and in the blood on the addition of a small amount of alkali to it. The blood in this case gave 0·008 per cent. of trimethylamine. The urine for twenty-four hours preceding death was obtained by a catheter, and gave a total trimethylamine content of 0·0033 grm. The post mortem in this case showed a condition of acute supervening on chronic nephritis.

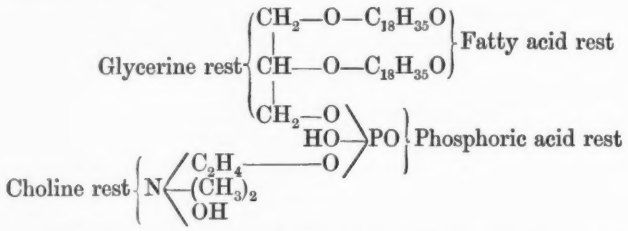
*Case III.* The blood was taken from a patient lying in a state of uraemic coma two days before death. On the two days preceding the venesection he had had violent epileptiform convulsions. The smell of trimethylamine was well marked. The blood gave 0·011 grm. per cent. of trimethylamine. The urine on the day that the blood was taken gave a total of 0·0075 grm. of trimethylamine for the twenty-four hours. The post-mortem appearances were those of an acute nephritis. A portion of the brain pounded up into an emulsion with normal saline, and treated by the Filippi process, gave distinct traces of a platino-choride resembling that obtained from the blood, and unweighable traces of the same salt were also obtained from the liver and spleen. All the organs emitted a well-marked smell of trimethylamine when pounded up with dilute NaOH.

*Case IV* was a boy who had been admitted into the hospital for chronic parenchymatous nephritis and developed a well-marked uraemic rash shortly afterwards. When seen he had typical disturbances of breathing and a well-marked smell of trimethylamine in the breath. The urine was scanty and high coloured; it contained some albumin and a trace of blood. He remained two weeks in this condition, having occasional comatose attacks, and during the last week of life he had two fits. It was not deemed expedient to bleed him, but Dr. Ewart, under whose care he was, kindly permitted me to estimate the trimethylamine in his urine, and kept him on a constant milk diet, which he took well up to the last. The amounts of twenty-four hours' urine taken every second day for a fortnight varied between 650 and 500 c.c., only sinking as low as 425 c.c. on the penultimate day of life. The blood trace was not found after the second day. The trimethylamine was fairly constant in amount, remaining about 0·04 grm., increasing to 0·05 and 0·054 grm. on the last two days of life. No post mortem was performed, but the clinical evidence left no doubt but that the case was one of uraemia.

An attempt was made to estimate the trimethylamine in the breath of this patient. He was provided with a well-fitting mask with an air inlet guarded by an expiratory valve. The expirations were directed through a one-inch tube fitted with a valve in the expiratory sense and passed through a very large Wolff bottle containing 0·25 per cent. HCl, the expired air being bubbled through about 200 c.c. of this. After three hours the acid was titrated, and a diminution of acidity which might have corresponded to a total amount of 0·001 grm. of trimethylamine in the air was determined. This was most certainly not really due to the excretion of anything like this amount of trimethylamine. A second portion of the acid gave a dubious trace of platino-chloride salt when treated after Filippi's method, and apart from a possible error of experiment the breath probably contained some free ammonia. No definite conclusions could be drawn from this experiment, though the smell of the breath left little doubt in my mind of the presence of trimethylamine.

It would appear from the evidence quoted above that there is a considerable increase of trimethylamine in the blood of uraemics. That such an increase is not due to the retention of trimethylamine may be inferred from the fact that no diminution of trimethylamine excretion was noted in the cases of nephritis,

and in the uraemic there was a slight increase of the daily output. It has been already mentioned that no smell of trimethylamine was noted in the breath of cases of ureteral obstruction. In one such case, when death followed a double impacted calculus, the blood was collected post mortem and examined for trimethylamine, and a normal value of 0·0018 was found. It would appear to be reasonable to suppose that the trimethylamine must have arisen in the uraemic cases from some body possessing the appropriate molecular grouping which was subjected to an abnormal metabolic process. The body that we should naturally suspect of being a precursor of trimethylamine would be lecithin. Our knowledge of the chemistry of the lecithin group is still in a very unsatisfactory state. The formula given below is some indication of the constitution of lecithin, which is in this case the distearyl-lecithin.



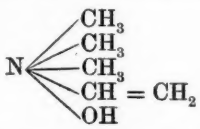

Through the saponification of lecithin with alkali fatty acids, glycero-phosphoric acid and choline are obtained. Schwartz (51) showed that by the action of X-rays choline can be formed in the body from lecithin. Choline is trimethyl-oxyethylammoniumhydroxide, and may be split up in watery solution into ethyleneoxide and trimethylamine. That lecithin is readily absorbed from the intestinal tract has been shown by the work of many observers (52). Di Filippi, as has been stated, failed to obtain a marked increase on feeding with lecithin-rich diet. I also failed to notice any increase on administering the yolks of ten eggs to a patient on a diet of three pints of milk, cocoa, 10 oz. of bread, and potatoes. The whole question, however, requires re-investigation. In a case undergoing starvation treatment for gastric ulcer, which was kindly placed at my disposal by Dr. Rolleston, I found on the third day after the onset of starvation a twenty-four hours' excretion of 0·019 grm. of lecithin. 0·5 grm. of lecithin in sterilized oil was then injected subcutaneously three times in twenty-four hours. The trimethylamine excretion on the two following days was 0·015 and 0·019 grm., but of course little can be said about variations when such small amounts are involved.

That trimethylamine is a toxic body, and capable of inducing severe epileptiform fits, has been shown by many authors (53). It is, however, hard to believe, even allowing for long-continued action, that trimethylamine in the amounts demonstrated in uraemic blood is sufficient to account for the uraemic convulsions. Possibly the blood is not the best place in which to look for indications of uraemic poisoning, and I am at present engaged in an attempt to form some idea of the total amount of trimethylamine in the body of a uraemic patient. According to Husemann, ammonium chloride is more toxic

than trimethylamine chloride. About 1 grm. per kilo body-weight is the fatal dose of the latter for the rabbit. Beaumetz, in 1873, stated that 1 grm. of ammonium chloride proved fatal to a rabbit, while a fatal result was not obtained with less than 5 grm. of trimethylamine chloride. Choline was found by Buzzard and Allen (54) to be more toxic than is generally supposed. Convulsions were caused by intraperitoneal and subdural injections. It has been pointed out, however, by many authors, that its toxicity is not great. In one of my cases of uraemia I obtained a somewhat dubious reaction in the cerebro-spinal fluid which appeared to correspond to Rosenheim's (55) test for choline, but I failed to find choline in the blood of the same case. Carrière (56), however, failed to find choline in uraemic cerebro-spinal fluid. Choline may probably be looked upon rather as the result of nervous tissue destruction than as an excitant cause of epileptic convulsions. Donath's (57) results in epileptic cerebro-spinal fluid are confirmed by Rosenheim's method. The great argument against considering choline as playing a part in the pathogenesis of uraemia is, apart from its low toxicity, the fall of blood pressure that has been shown to follow its injection by Mott and Halliburton (58), whereas the onset of acute uraemia has generally been found to be associated with a rise of blood pressure.

The far more toxic neurine is closely related to trimethylamine.

Neurine is trimethylethylvinylammoniumhydroxide.



Neurine has been shown by Mott and Halliburton to affect the heart, cause contraction of the peripheral vessels with a considerable rise of blood pressure, and to have a curare-like action on muscles.

The absence of the increase of trimethylamine in the blood of cases suffering from obstructive urinaemia will, if confirmed, be a valuable additional support to the attempts made to differentiate between the conditions of urinaemia and uraemia, conditions which, as we have already seen, have been shown to be widely apart in certain clinical aspects.

A brief review of our knowledge of the pathology of uraemia would be incomplete without some reference to the possible relation of the internal secretions of the kidney, and of the part played by the cytotoxins of the kidney in the current theories of uraemia. Brown-Séquard (59) showed, and Ascoli has confirmed the fact, that animals after double nephrectomy die sooner than after simple ligature of the ureters. As in each case the retention of the potential urinary constituents is essentially the same, it has been thought that the earlier death of the doubly nephrectomized animals arose from the absence of some internal secretion on the part of the kidneys. It would appear, however, that this conclusion is not necessary. The kidney may have the power of converting into a harmless compound some otherwise toxic constituent of the

blood, and though this may not be actually carried away by the ureters, sufficient of it may be transferred to the renal tubules and parenchyma to prolong the in any case very short life of the animal with ligature of the ureters, over that of the animal with double nephrectomy. This objection would, however, appear to be negatived by the results obtained by the injection of kidney extract or normal serum into the nephrectomized animal.

Such an injection is followed by a great improvement of the condition, and Meyer (60) has noted that when Cheyne-Stokes respiration has set in, this may be inhibited by the injection of an emulsion of normal kidney. Numerous observers (61) have found that the kidney contains a substance raising the blood pressure on injection, and the same hypertensive substance has been demonstrated physiologically in blood coming from the renal veins. Lignerolles and Lawes, and more recently Teissier (62), have employed serum from the renal vein in the treatment of acute nephritis, and found that it relieves uraemic dyspnoea and increases the urea output, and at the same time paradoxically it has been found to diminish the toxicity of the urine while causing a general improvement in all the symptoms. The property of increasing the urea output claimed for the blood from the renal vein is apparently inconsistent with the observation of Bradford (63) that ablation of four-fifths of the kidney substance gave rise to an increased secretion of urea. If also it be want of the hypertensive substance in the renal extract that causes the symptoms of uraemia, it is hard to see how it comes about that uraemia is generally held to be associated with an increase in the blood pressure such as has been observed by Forlanini, Riva Rocci and Pedrazzini, and many others. The possible explanation may be that the rise of the blood pressure is a defensive mechanism on the part of the kidney and is brought into play as a last effort to induce an efficient urinary secretion. This view fits in well with the clinical commonplace that when the heart of acute nephritis hypertrophies sufficiently to raise the blood pressure considerably, the amount of urine passed begins to increase and the danger of uraemia is over.

Another explanation of the uraemic syndrome from a widely different point of view, is that the uraemic intoxication is due to the entrance of nephrolysins from the damaged kidney into the blood-stream. It is hardly necessary to enter into a discussion of the literature that has grown up around this subject (64), or to inquire how far the products of the autolysis of the kidney are likely to exercise a cytolytic action on cells of other tissues in the same organism. It is sufficient to recall the fact that uraemia is not a symptom complex attending extensive destruction of the kidney substance taking place at the same time, but may make itself felt equally when the strain on the organism from the renal inefficiency of chronic interstitial nephritis reaches its breaking-point, and such cases are certainly unconnected with any recent diffuse autolysis of kidney tissue.

We have reviewed a number of theories without finding any explanation of decisive value of the uraemic syndrome. The trend of modern work tends more and more to free us from the conception of urinary retention as a cause of uraemia, a conception which in the past has diverted a great mass of labour

into barren tracts. It seems to be increasingly important to fix the attention on the alterations of general metabolism. It is by the study, from the chemical point of view, of any body that appears in the organism in uraemia and that cannot be accounted for on the supposition of its being a mere retention product that we may hope to obtain an insight into the abnormalities of uraemic metabolism. Such a body is ammonia, which, as the acute mind of Frerichs realized years ago, must owe its presence to some abnormal elaboration of the nitrogen katabolic products before they reach the kidney; and trimethylamine, which has been dealt with at what might be undue length in a review were it not that the evidence here presented is, as far as I know, original. Whether we must look to these bodies or to their precursors for the explanation of the toxic effects it seems clear that in future attention must be given to the tissues just as much as to the blood in chemical research.

In conclusion it may be allowable once again to urge that, notwithstanding the apparent confusion of the uraemic symptom complex, the evidence of a specific toxaemia of the nervous system is sufficiently strong to make it imperative to exhaust all methods of identification of a specific uraemic poison before resigning ourselves to the theory of multiple intoxication and general breakdown that has been so much put forward of late as a cloak for the bareness of the pathological researches on uraemia.

The bibliography appended is of course incomplete as to uraemia, and simply represents such papers as are referred to in this essay.

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## ERRATA

PAGE 192. The reference under Petechioid Eruptions to Plate 11, Fig. 10 *should read* Plate 11, Fig. 9.

PAGE 194. Under Petechial Eruptions, Plate 11, Fig. 9 *should read* Plate 11, Fig. 10.

PAGE 195. Under Vesicular Eruptions, Plate 11, Fig. 10 *should read* Plate 10, Fig. 8.

PAGE 212. In the Description of Plates, Plate 10, Fig. 8 *should read* Petechioid eruption showing small vesicles; Plate 11, Fig. 9 *should read* Petechioid prodome; and Plate 11, Fig. 10 *should read* Petechial prodromal rash.

[*Q. J. M., April*, 1909.]

# BRONCHIOLECTASIS IN CHILDREN

## WITH REFERENCE TO THE CONDITION KNOWN AS HONEY-COMB LUNG FROM A CLINICAL STANDPOINT[1]

By ERNEST LEACH

With Plate 13

Bronchiolectasis in children is not uncommonly found as a sequela to broncho-pneumonia complicating an attack of measles or whooping-cough. That the condition is non-tuberculous is shown by the maintenance of the general nutrition, the marked lowness of the temperature (in many cases the temperature remaining normal), the absence of night sweats and of tubercle bacilli from the sputum, the negative results to Calmette's reaction, and post-mortem examination. In some instances a secondary tuberculous infection takes place.

### A Report of Five Cases.

*Case I.* E. W., male, aged 1 year, October, 1905.

*Previous History.* Two months previous to admission the child had an attack of diarrhoea and vomiting accompanied by bronchitis. This was followed by measles and pneumonia. From this time the child had had a cough which had got worse during the last fortnight. There was no family history of phthisis.

*On examination* the chest was normal in shape and moved equally on the two sides. The apex-beat of the heart was not displaced. Over the right side in front the note was impaired from the third rib, flat at the level of the fourth rib, and dull from below the fifth rib in the axilla and the seventh rib in the scapular line. Vocal resonance and fremitus over this area were increased. The breath-sounds were well heard, also a few crepitations. A few rhonchi were heard over the rest of the lung in front. The temperature was 98·8° F.; pulse-rate, 120 per minute; respirations, 40 per minute.

October 16. The temperature had risen to 102° F. An aspirating-needle was inserted in the posterior axillary line on the right side and nothing but blood was obtained.

October 18. The respirations were very rapid, the rate being 84 per minute, the temperature was 101·8° F., and pulse-rate 168 per minute. On the right side of the chest above the area of impaired resonance some coarse crepitations were heard; over the dull area in front the breath-sounds were very loud, high-pitched and echoing in quality, and coarse crepitations were heard. The same condition was found behind. On the left side the lower two-thirds of the chest showed loud crepitations. Marked cyanosis was present.

October 26. The physical signs were unchanged, but the temperature had

[1] Part of a thesis presented at Oxford University for the M.D. degree.

fallen to 98° F., and the respirations to 42 per minute. The condition remained unaltered except that the temperature rose again, until death ensued on November 13. No tubercle bacilli were found in the sputum.

*Post mortem.* The body was plump and well nourished. No signs of tuberculosis were found. There were firm pleural adhesions at both bases and involving the interlobar fissures. Diffuse broncho-pneumonia was present with small cavities, which were most marked in the lower lobes but not limited to these. These cavities were similar in all respects to those found in a honeycomb lung, but they did not present beneath the pleural surface. Microscopically they were related to the bronchioles.

*Case II.* F. A., aged 2 years, October, 1888. There was a previous history of measles and one of the family had recently died from diphtheria. The child was taken ill with diphtheria and admitted to hospital. No physical signs of disease were present in the lungs. The child died on October 23.

*Post mortem.* The lungs were pale and curiously dotted with black pigment-spots. These were hard to the touch and the centre of each was occupied by a small bronchus. The bronchioles were everywhere dilated. The affection appeared to be a chronic peri-bronchitis with bronchiectasis, but scattered here and there through the lung were what appeared to be miliary tubercles. Microscopically there was seen an acute peri-bronchitis accompanied by extreme bronchiectasis. A certain amount of acute interstitial pneumonia was present, apparently spreading from the peri-bronchial inflammation, also a small amount of emphysema. The walls of most of the finer bronchi were infiltrated with leucocytes which invaded the peri-bronchial connective tissue in great numbers, forming a solid circular mass, the centre of which was pierced by the dilated lumen of a bronchus. From this as a centre the leucocytes invaded the walls of the surrounding alveoli, but those at a distance from the bronchi were but little altered. No tubercles were seen.

*Case III.* W. C., aged 4 years, May, 1893. There was no history of illness up to two months before, when the child was attacked with cough, expectoration of thick phlegm, and sickness three or four times a day. These symptoms got gradually worse and he got weaker, though he went to school up to the day before his admission. On admission his face was flushed and his respiration was very rapid and wheezy, with occasional cough. There was no marked dullness on percussion. Numerous crepitations were heard over both lungs. No tubular breathing was heard. The pulse-rate was 136 per minute, respiration 44 per minute, temperature 103·6° F. After a few days the temperature came down to normal and remained there. The boy was very cyanosed, and the respiration-rate varied between 40 and 60 per minute. On June 3 subcutaneous emphysema was found over the neck, cheeks, abdomen, back, and arms as far as the wrists. On June 8 the boy was deeply cyanosed; the pulse-rate was 120 to 140, respiration-rate 50 to 60, and the temperature 97° F. Little change occurred in his condition up to the time of his death on June 19.

*Post mortem.* The lungs were very bulky; their surfaces were thickly strewn with small, round, transparent, bladder-like elevations. On section both lungs showed a similar condition; a number of small cavities, the largest about the size of a pea, were scattered through the organs, giving them a worm-eaten appearance (honeycomb). These cavities had perfectly smooth walls and were either empty or full of frothy mucus, being most thickly distributed under the pleural surfaces. The larger tubes were not dilated and showed no signs of disease. In both lungs patches of broncho-pneumonia were present, all of small size. There were no signs of tuberculosis. The bronchial glands were healthy. The right ventricle of the heart was greatly dilated and hypertrophied. Microscopically there was widespread but unequally distributed acute bronchitis with peri-bronchitis, interstitial broncho-pneumonia, and pulmonary collapse.

The bronchioles were extremely dilated and their walls thinned. There was considerable emphysema.

*Case IV.* G. F. W., aged 27.

*Family History*: unimportant. *Previous History*: he had had bronchitis at three months old. Since that time the man had had bronchitis and cough every winter, which usually improved during the summer months, but during the summer of 1906 the cough did not leave him. There had been one attack of haemoptysis sixteen years before. For a large number of years since he was quite a small child there had been a copious expectoration of a thick yellow mucus.

The patient was an emaciated man with considerable dyspnoea with orthopnoea, the respiration-rate being 32 per minute. He was distinctly cyanosed. There was frequent cough with expectoration of a large amount of very offensive sputum. Marked constriction of the chest was present. The fingers and toes were clubbed. Over the lungs in front the note on the left side was flat from the level of the second rib and more impaired in the axilla. The breath-sounds were high pitched and numerous, and a large number of crepitations were heard. Behind, the movement on respiration was almost absent. Vocal fremitus and resonance were increased over the left lower lobe. The percussion note over the whole of the left side was dull and impaired from the level of the fifth rib downwards on the right side; over this area the breath-sounds were very feeble. Over the left side the breath-sounds were harsh and numerous consonating crepitations were heard. The temperature ranged between 100·2° and 101·4° F. Death occurred on January 7. No tubercle bacilli were found in the sputum.

*Post mortem.* The bronchial glands were inflamed but there was no trace of tuberculosis. The right lung was emphysematous and encroached on the left, being slightly adherent at its base. On removing the front of the thorax a large abscess $1\frac{1}{2}$ inches in diameter, situated in the anterior part of the right lower lobe, was torn open. The rest of the right lung was emphysematous and oedematous. A second abscess cavity was found above and behind the previous one, being three-quarters of an inch in diameter. The left lung was universally adherent and retracted but could be easily shelled out. The pleura was slightly thickened. On section the lung was typically honeycomb throughout, the larger cavities, nearly an inch in diameter, being situated at the margin of the lung. The excavation was uniform in all parts of the lung, and the trabeculae of connective tissue between the larger cavities were riddled with smaller cavities. Microscopically there was no evidence of tuberculosis. An extreme degree of chronic inflammation of the pulmonary tissue was present. The alveolar walls were greatly thickened, and in some places dilated and in others collapsed. The small and capillary bronchi were very much dilated and their walls replaced by inflammatory tissue.

*Case V.* A. H., male, aged 19, October, 1905.

*Previous History.* He had had rheumatic fever at five years of age; whooping-cough and measles followed by bronchitis when quite a small child. From this time he had always had a bad cough with expectoration of a large amount of sputum. The amount of expectoration had increased considerably during the last four years. It was stated that he had had an attack of haemoptysis when at school at the age of four. He was in St. Thomas's Hospital for his cough at the age of nine and again in 1904. The expectoration was offensive and was coughed up three or four times a day. In the intervals he remained fairly free from cough. The cough and expectoration were produced by change of posture or on stooping down. He had brought up blood on several occasions, the amount being two or three ounces at a time. Since he was discharged from hospital in February, 1905, he had remained fairly well, but he

had a sharp attack of haemoptysis in May, when he lost about a pint of blood and was unconscious for a quarter of an hour. He had gained weight considerably up to six weeks ago, and on readmission was 6 lb. heavier than when he left the hospital.

*On examination* there was marked clubbing of the fingers. The knees and wrists were slightly swollen. Pulse-rate 80 per minute; temperature 97·8° F. In the examination of the chest the sub-costal angle was somewhat constricted. The left side appeared smaller than the right, the movement with respiration on this side being almost entirely absent. The left side of the chest measured on expiration 15½ inches, on full inspiration no change; the right side on expiration measured 14 inches, on full inspiration 15 inches. The heart was displaced into the left axilla. The apex-beat was diffuse, but the point of maximum intensity was situated in the seventh space, one inch posterior to the mid-axillary line. Systolic retraction was present at the apex. Cardiac dullness began above at the level of the fifth rib and extended inwards to within one inch of the nipple line. The heart-sounds were not altered. The percussion note was everywhere more or less impaired. Absolute dullness was present at the left base behind below the level of the sixth rib in the scapular line; this area of dullness extended outwards and became continuous with the area of cardiac dullness. At the left apex the note was impaired. Vocal fremitus was increased over the left apex front and back, but much diminished at the left base behind. On the right side the breath-sounds were harsh and a few rhonchi heard. At the left apex the breath-sounds were distant and expiration was prolonged. Just below the angle of the left scapula loud cavernous breathing with metallic crepitations was heard. Whispering pectoriloquy was obtained. Below this the breath-sounds were absent. Urine, specific gravity 1018, alkaline, heavy cloud of albumen, no sugar was present.

November 10. An attack of haemoptysis occurred during sleep and without cough; about 15 oz. of blood were brought up. Previous to this the amount of expectoration varied from 10 to 20 oz. per diem and was usually tinged with blood.

December 11. The weight had increased 1½ lb. during the previous six weeks. The amount of expectoration had decreased to a few ounces per diem. The patient was getting up every day.

December 28. There had been a gain in weight of 3½ lb. during the previous fortnight. When he left hospital on January 27, 1906, the right side of the chest on inspiration measured 15 inches and on expiration 13½ inches; the left side measured on inspiration 15½ inches and on expiration 15 inches. He was much improved and the amount of expectoration was quite small. He was readmitted on June 6, 1906, having had several bad attacks of haemoptysis between May 28 and June 3. The amount of expectoration had increased considerably. The temperature was 98·8° F. and the pulse-rate 120 per minute. The physical signs were not changed from those described above. On June 3 on getting up he complained of weakness down the left side (for three days previous to this he had suffered from headache) and later in the day had two fits. Paralysis of the left arm and leg gradually ensued. On June 24 he was trephined and an abscess involving most of the right motor area was found. About an ounce of foetid pus was evacuated and the cavity drained. The physical signs in the chest remained unaltered and death ensued on July 7.

*Post mortem.* The right lung was in a state of compensatory emphysema and entirely covered the anterior aspect of the pericardium. No adhesions were present on the right side. The left lung was lying against the spine completely collapsed, and was bound to the parietes and pericardium by very dense adhesions which were torn through only with the greatest difficulty. On section there was universal dilatation of the bronchi and bronchioles, both saccular and cylindrical, with fibroid airless lung intervening. Beneath the pleural surfaces irregular

cavities had formed into which the bronchial tubes opened. The walls of these cavities were lined with a ragged epithelium and they contained a quantity of foul-smelling secretion. The bronchiectasis affected both lobes to an equal extent. The bronchial glands were enlarged and inflamed, but no evidence of tuberculosis was present either in the glands or elsewhere.

### The Naked-eye and Microscopical Appearance of a Honeycomb Lung.

The lungs present a remarkable excavated appearance to which the name honeycomb has been most appropriately applied. In some cases the condition is bilateral, in others the whole of one lung may be affected, in others again the whole of a lobe or only a portion of it. The cavities in the lung in all cases present a similar appearance; they are multiple, more or less spherical, often communicating with each other, and are divided off by bands and septa. They vary in size, some being as large as a good-sized pea or larger, depending on the length of time the condition has been present in the lung, the larger cavities being situated nearer the periphery of the lung. These cavities may be empty or may contain a purulent secretion. The visceral pleura more often than not is non-adherent to the parietes and bullae project as small bladder-like elevations from the surface of the lung, the lining membrane being smooth and opaque.

With the aid of a microscope the following points can be made out in a recent case. (1) Some of these cavities are clearly dilated bronchioles, since they are lined by columnar epithelium and there are muscle and elastic fibres in their walls. The walls of these smaller bronchi are in many places in a state of acute inflammation with small-celled infiltration, and an extensive destruction of their elastic coats is in progress. Many of the bronchioles are plugged with masses of inflammatory exudation, whilst others have lost their lining epithelium. Peri-bronchial inflammation can also be seen. (2) Other cavities are being formed by the distension of the atria and infundibula, as is shown by their scalloped or crenated outlines and their communication with the bronchioles. (3) Other larger cavities than the above are present, the walls of which consist entirely of inflammatory cells and the spaces appear sharply punched out. They have no epithelial lining, but some have their walls lined with a layer of inflammatory lymph. These cavities are bounded by collapsed alveoli which may show signs of considerable inflammation. In some parts the spaces can be seen in the process of formation and are clearly due to the breaking down of broncho-pneumonic patches. If the softened material is discharged through a bronchiole, a cavity is formed, which by a process of inflation becomes spherical and increases in size.

In some cases the wall of the cavity was lined by columnar ciliated epithelium. It is to be assumed that these were bronchiolectases, since the ciliated epithelium ends at the termination of the lobular bronchioles. In many cases in which there was no evidence of tuberculosis, giant cells have been found in the walls of some of the cavities. The presence of giant cells has been

described as being a common occurrence in broncho-pneumonia, and possibly they may be derived from the alveolar epithelium. The cavities are seen thus to be of three kinds:—

(*a*) Some dilated bronchioles or a true bronchiolectasis.

(*b*) Some due to dilatation of the atria and infundibula, hence atriectases and infundibulectases with emphysema.

(*c*) Some are abscess cavities which have discharged their contents into a bronchiole and have become enlarged by a process of inflation.

### Views on its Causation.

Various theories have been advanced. Sharkey has described the condition as an acute bronchietasis of the smaller tubes, and on this assumption the term bronchiolectasis was applied to it. This no doubt is in part correct, and some of the cavities, as has been pointed out, are due to the dilatation of the smaller bronchi which the term implies. The bronchioles, however, do not reach to the periphery of the lung, but expand to form an atrium which itself has two or three openings into the infundibula; thus it will be seen that the bullae which project on the surface of such a lung cannot be formed by the dilatation of a terminal bronchiole, but are due to the dilatation of an atrium or an infundibulum. H. H. Tooth summarized the condition as follows: that the vesicles, though large in number, are relatively few compared to the normal alveoli, that in every case the cavity is surrounded by inflammatory material indistinguishable from peribronchial inflammation; and put forward the following suggestions:—(*a*) that the cavities are due to the destruction of the walls of the neighbouring alveoli—a form of emphysema, (*b*) that they are dilated bronchioles, or (*c*) a combination of the two.

Rolleston and Kanthack, who examined Tooth's specimen, were of opinion that the cavities were not bronchiectases, but were vomicae formed by the breaking down of broncho-pneumonic masses, that is, were abscess cavities in communication with the bronchioles.

This is in accord with the opinion of Trousseau, Bristowe, and Gardner. Carr, following the traction theory of bronchiectasis, suggests that in some cases the tough pleural and pericardial adhesions being present may, by an inward extension of the fibrotic process into the lung, give rise to a secondary dilatation of the tubes. He points out that chronic bronchitis weakens the elasticity of the bronchial walls, and that catarrhal pneumonia is always accompanied by dilatation of the tubes, which is increased by the strain at the commencement of each cough before the glottis is forced open: this dilatation allows secretion to collect, perpetuating the inflammation, which spreads to the interalveolar connective tissue and sets up fibrosis. This fibrotic tissue contracts and further helps to drag the bronchial walls apart.

This theory of the part played by the inward spread of the fibrotic process from the pleural adhesions could be entertained were it possible to show that in

all the cases of honeycomb lung dense pleural and pericardial adhesions were present; but this is not so, and in the majority of cases no pleural adhesions are present, in others the adhesions are so few that they could not be held responsible for producing this condition of the lung.

Miller, in a recent communication, thinks the accumulation of secretion, the cough, and the loss of support of consolidated lung tissue causes dilatation of the smaller bronchioles, the muscular and elastic coats of which have been destroyed by acute inflammation of their walls.

Two cases have been reported, one by Morley Fletcher and one by Bernstein, in which the honeycomb lung was present, and in addition the smaller bile-ducts were inflamed and dilated. Bernstein suggested that possibly an autogenetic toxin was produced by the intestine and conveyed thence to the liver and secondarily to the lungs.

C. R. Box has shown that the cavities in a honeycomb lung arise, as already indicated, in three ways, some being bronchiolectases, some dilated atria with emphysema, and some formed by necrosis of lung tissue; he holds that the formation of a honeycomb lung is due to broncho-pneumonia. He further states that on comparison of a honeycomb lung with a saccular bronchiectasis in an adult it appears that the latter is only an advanced condition of the former, since the shape of the cavities, their arrangement and communications, are similar, except that in an adult the walls and septa are thicker and the lining membrane more opaque owing to long-continued chronic inflammation.

Granted that honeycomb lungs and chronic saccular bronchiectases are one and the same condition, the result of antecedent broncho-pneumonia, the question whether the causative broncho-pneumonia is ever tuberculous naturally arises. No doubt it may be. At the same time Box has pointed out that all the evidence available goes to show that the chronic cases are not cases of chronic pulmonary tuberculosis. He holds that those cases which originate in a tuberculous broncho-pneumonia run a comparatively rapid course and terminate fatally before the disease can become chronic. He has never been able to prove the presence of tubercle bacilli in the sputum from a chronic bronchiectasis in a child, and since the introduction of Calmette's test he has applied it to as many of his old patients as could be traced. The reaction has been absent in twelve out of fourteen cases.

## The Clinical Aspects and Physical Signs.

The *Clinical History* almost always dates from an attack of measles, whooping-cough, or broncho-pneumonia. On making careful inquiries into the history of each case the onset of cough can be traced back sometimes for a long period of years to an attack of measles or whooping-cough which has been complicated with bronchitis or broncho-pneumonia.

The symptoms in children with bronchiectasis are cough, dyspnoea, and

copious expectoration. Clinically the cases may be divided into three classes:—(1) Those in which the honeycomb lung is present and in which death has occurred from some independent disease, the condition being probably due to some antecedent lung inflammation which has subsided. In this class of cases there may be no physical signs of the disease and the condition will unexpectedly be found post mortem. (2) Those cases in which there is considerable broncho-pneumonia coexisting with the honeycomb lung, the physical signs in such cases being those of broncho-pneumonia and usually most marked behind at the bases of the lungs. Cavernous signs may be present at one time and not at another, depending entirely on the amount of pus in the tubes of the lung. (3) Old-standing cases in which shrinking of the lung, dislocation of the heart towards the affected side, clubbing of the fingers, and signs of venous back pressure may have developed.

The constriction of the chest walls may be restricted to the zone below the nipple on the left side or may be bilateral at the bases. Exceptionally it is apical.

Most of the cases described have been left-sided and basal; a possible explanation of this may be that the left bronchial tree is longer than on the right side, and thus there may be more difficulty in expelling the contents of the bronchial tubes on this side.

*The Physical Signs in the Third Class.* These vary according to the amount of secretion present in the tubes and cavities of the lung. If the tubes are full, the vocal fremitus and resonance will be diminished, the percussion note will be dull, and the breath-sounds diminished, or absent; the signs being practically the same as in a case of pleurisy with effusion, but differing in this respect that the chest is contracted and the heart, instead of being pushed away by the effusion, is pulled over towards the affected side.

In many cases the situation of the apex-beat of the heart is not altered. If, on the other hand, the tubes are empty or emptied by coughing, or by inserting a spatula at the back of the throat to produce coughing, or better still by inverting the child, a marked change in the physical signs is found. The vocal fremitus and resonance are both increased and whispering pectoriloquy may be obtained; the percussion note is impaired, but is not of the same dull character as when the tubes are full of secretion. The breath-sounds are louder and are often tubular or cavernous in character. Patches of tubular or cavernous breathing may be heard over the same lobe of a lung affected with the condition. Numerous consonating crepitations will be heard and possibly some rhonchi. The change in physical signs may be quite out of proportion to the amount of purulent expectoration coughed up, in which case it is probable one of the larger bronchi is blocked up by a plug of secretion preventing any air-entry into the lower ramifications of this bronchial tube.

*Cough* is very noticeable and is often paroxysmal, usually being present winter and summer. There is often a frequent desire to cough but the inability to do so until the child has been inverted—by this means the secretion passes

by gravity down the tube to the main bronchi, gives rise to an attack of coughing, and is expectorated, with much relief to the child. The cough is usually worse at night-time soon after going to bed and on getting up in the morning, a large amount of secretion having collected in the tubes during the hours of sleep. *Haemoptysis* is not an uncommon occurrence. The *expectoration* varies in amount, but usually is considerable in quantity, consisting of tenacious pus of a greenish tinge. In most cases it is odourless, but in long-standing cases there may be a very foetid smell with it, especially when sepsis has supervened. In almost all the cases a careful clinical examination was made with regard to the presence of tubercle bacilli, but in none of the cases were they discovered. The *temperature* may or may not be raised. It is a striking point in this condition how little fever there is present in comparison with the large amount of pus contained in the tubes of the lung. A rise of temperature to 100° or 101°F. usually denotes recurrent pulmonary inflammation. The *nutrition* is well maintained as a whole. This is in marked contrast to cases of chronic pulmonary tuberculosis, in which the opposite condition prevails. *Clubbing* of the fingers and toes is more or less marked in this condition, as in all chronic pulmonary diseases. The view of the chest under the X-rays depends entirely on the amount of secretion present in the tubes of the lung. If the bronchi are full of the secretion a dark shadow will be thrown on the screen and at the same time the movements of the diaphragm can be ascertained as well as its level. *Dyspnoea* is especially noticeable on exertion or even when the child is at rest, the breathing being shallow and rapid.

*Complications.* The commonest is recurrent pulmonary inflammation, either bronchitis or broncho-pneumonia; pleurisy of the adhesive kind may occur. Other complications are rare, such as pneumothorax, mediastinal emphysema, or subcutaneous emphysema; the latter may start from the mediastinum or from an exploratory puncture. In the latter case adhesive pleurisy is present, and the air is pumped into the planes of subcutaneous connective tissue and may spread all over the body. Other rare complications are subacute inflammation of the joints, suppurative meningitis, cerebral abscess, lardaceous disease, empyaema.

Death usually results either from an acute pulmonary inflammation, or later on from sepsis. Tuberculosis may possibly develop.

My thanks are due to Drs. Sharkey, Acland, Hawkins, Turney, and Box, for kindly allowing me to publish the cases under their care.

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## DESCRIPTION OF FIGURES.

### PLATE 13.

FIG. 1. A section of a lung showing numerous cavities, giving the whole a 'honeycomb' appearance (St. Thomas's Hospital Museum).

FIG. 2. The outer surface of a lung showing bullae projecting on the pleural surface (St. Thomas's Hospital Museum).

FIG. 3. A section of 'honeycomb' lung from a young adult. Many of the cavities are lined by columnar epithelium. The surrounding chronic inflammation is well shown (low power).

FIG. 4. High-power view of one of the cavities, showing the columnar epithelium lining the cavity.

FIG. 5. Section of 'honeycomb' lung from a case of tuberculous broncho-pneumonia. The cavities are sharply punched out and their walls consist of inflammatory cells. These cavities are being formed by the breaking down of broncho-pneumonic masses.

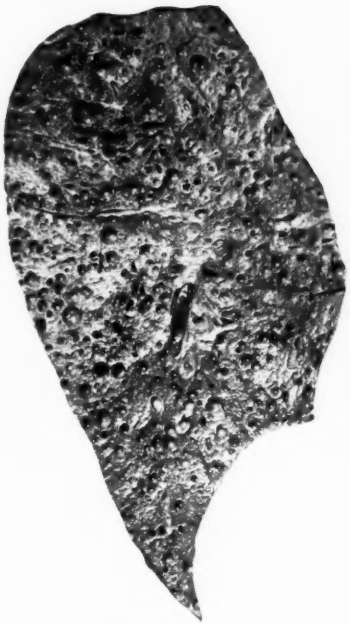

FIG. 1.

FIG. 2.

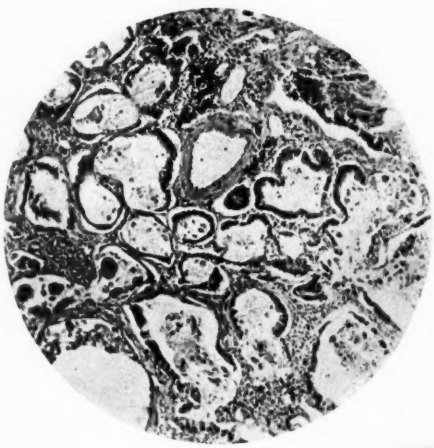

FIG. 3.

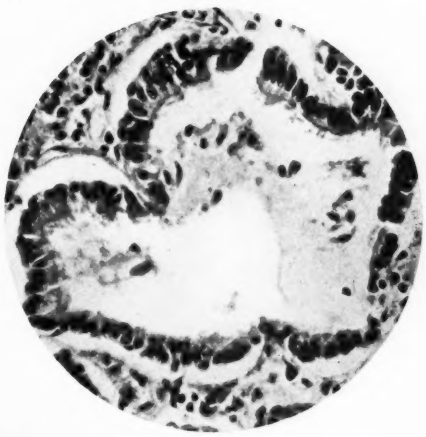

FIG. 4.

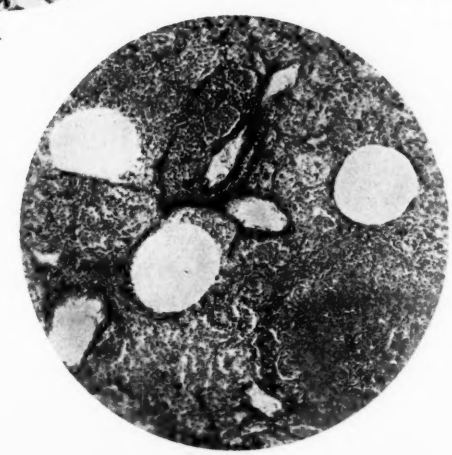

FIG. 5.

# VASO-DILATORS IN HIGH BLOOD PRESSURE

By EDWIN MATTHEW

Haemomanometric observations have added to our knowledge of the pulse and blood pressure, estimations set out in actual figures being a valuable addition to the digital examination and sphygmographic records of the pulse.

These estimations are of chief importance when the blood pressure is increased. A rise in blood pressure may be, and often is, beneficial, but in consideration of the fact that it is always followed by a tendency to further rises that will be harmful, the methods at our disposal of keeping the pressure within bounds are of prime importance.

In addition to regulations as regards methods of living, of diet, of exercise, &c., we can assist by internal medication of various kinds.

For the past two years I have, in Leith Hospital, been engaged in investigations on abnormal blood pressure, and in addition have made a large series of observations with various substances, to ascertain, if possible, their action and benefits, or otherwise, in the numerous cases of hypertension that had come under observation. Of these substances the best known are the various nitrites and organic nitrates. For long their vaso-dilator action has been known and therapeutically employed. Their action has been investigated physiologically on animals, and clinically by observations on the pulse with the finger and the sphygmograph. These methods undoubtedly convey a considerable amount of information, but it cannot be maintained that the results are at all comparable in exactness and comprehension to exact blood-pressure readings. Something definite is conveyed to the mind by exact numbers, and the knowledge that a blood pressure measures 150 millimetres of mercury is more satisfying than a report that the pulse tension is slightly, moderately, or markedly increased.

So far as I am aware this has not been done, and my purpose has been by actual sphygmomanometric observations exactly to determine the individual and relative actions of the various nitrites and other substances in conditions of high blood pressure.

Much work has been done clinically and experimentally on the various nitrites. Cash in his investigations was able definitely to group them as regards promptness of action and lasting effect, and subsequently several of them were used clinically, through the writings of Brunton and others. Amyl nitrite and nitro-glycerine appeared active vaso-dilators, but though producing a very speedy and powerful action, their evanescent nature militated against their having more than a very limited use.

[Q. J. M., April, 1909.]

Numerous observers then undertook a series of investigations to obtain if possible a substance having a less powerful but more prolonged action.

Matthew Hay experimented with ethyl nitrate and allied bodies, but concluded they were of no practical use. Leach investigated the nitrates of the fatty series, and found all possessed dilating effects on the blood-vessels—generally of a prolonged kind. He suggested their use clinically, but found they were liable to cause headaches.

Lauder Brunton tried hydroxylamine hydrochlorate. It answered the purpose, but always caused gastric disturbance.

Bradbury from the higher valent alcohols was able to produce and investigate a series of nitro bodies. These were methyl nitrate, glycol (ethylene) dinitrate, glycerol trinitrate (nitro-glycerine), erythrol tetranitrate, and mannitol hexanitrate. Their activities, he found, varied within wide limits, due naturally to their different solubilities and liability to decomposition. Methyl nitrate he found the most soluble, but with a comparatively slight vaso-motor action. Glycol nitrate had a powerful action resembling that of nitro-glycerine. Erythrol and mannitol were less soluble, but their action was more prolonged. He recommended the use of the latter two bodies as likely to fulfil all requirements where more prolonged action was desirable than could be obtained with nitro-glycerine. The action of these nitrates he ascertained by perfusion observations on animals and by sphygmographic tracings in man.

My haemomanometric observations I have confined to the nitrites and nitrates that are in general therapeutic use, viz. nitro-glycerine and liquor trinitrini, sodium nitrite, potassium nitrite, erythrol tetranitrate, mannitol hexanitrate, and cobalto-nitrite of potassium.

I made no observations with amyl nitrite. Its action is so sudden as not to be easily ascertained by the instruments I worked with. By careful haemomanometric observations one is able to analyse the action of these nitrites under the following heads:—

1. The time the action begins after administration of the nitrite.
2. The amount of reduction in the blood pressure produced by a single therapeutic dose.
3. The time in which the maximum action is attained.
4. The time after which the action of the nitrite begins to pass off.
5. The time after which the blood pressure again regains its original level.

Having obtained these facts, it is possible to summarize the action of the individual nitrites, and also to form a comparison of their relative vaso-dilator effect.

### Methods of Observation and Investigation.

The instruments I employed were the Lockhart-Mummery and the Martin modification of the Riva Rocci apparatus with the broad 12 cm. Recklinghausen cuff. In addition, I used Dr. Oliver's two instruments with the spirit manometer. Dr. Oliver's spirit manometers give a somewhat higher blood-pressure reading than the mercury instruments to the extent of from 5 to 10 mm. For observations with vaso-dilators they all serve equally well.

My observations were all made with the patient in the recumbent position, and all were made at the same time of day, and at a time in the day when we know the blood pressure to be more or less constant. I chose the hours between 10 a.m. and 1 p.m., and so was able to avoid the possibility of diurnal variations and variations due to meals, the drugs being given on an empty stomach.

For several successive days before making an observation I estimated the blood pressure of the individual, partly to accustom him to the process and avoid the rise in pressure that occurs in those who are unaccustomed to the air-compression of the arm and whose mental condition is one of perturbation at the whole process.

On the day of administration of the nitrite I first of all estimated the blood pressure two or three times at short intervals. I then administered the drug and noted the time of administration. At fixed and successive intervals the pressure was taken and noted, and this was continued for varying periods until the effect of the nitrite had passed off or nearly so.

With the instruments I employed, the greatest ease and accuracy is obtained by working with the systolic pressure, and this method I employed in all my observations.

*Nitrites and Nitrates employed.*

1. Tabloids of nitro-glycerine and B. P. solution of liquor trinitrini.
2. Solution of sodium nitrite in water.
3. Solution of potassium nitrite in water.
4. Tabloids (Burroughs, Wellcome & Co.) of erythrol tetranitrate.
5. Chocolate tablets (Martindale's) of erythrol tetranitrate.
6. Chocolate tablets (Martindale's) of mannitol hexanitrate.
7. Cobalto-nitrite of potassium in powder.

I may say first of all that with tabloids of nitro-glycerine and of erythrol nitrate I was singularly unsuccessful in obtaining any depressor action. I was forced to conclude that the nitro-glycerine and the erythrol were either pharmacologically inert or that the tabloids remained undissolved. Even after hours of observation I obtained no action, a result never found if the nitro-glycerine or erythrol were given in a form easily absorbed—the former as liquor trinitrini and the latter in the form of chocolate tablets.

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## I. Observations with Liquor Trinitrini.

I made in all twelve observations in doses chiefly of 2 minims, and in one or two instances of 3 minims. The reasons for fixing on these amounts I will refer to later.

The results of these observations I can most easily indicate by means of charts, of which the two following (Figs. 1 and 2) are typical examples. They set out in detail the action of a therapeutic dose of liquor trinitrini in a suitable case.

1. *Time in which the blood pressure begins to fall.* Over the twelve

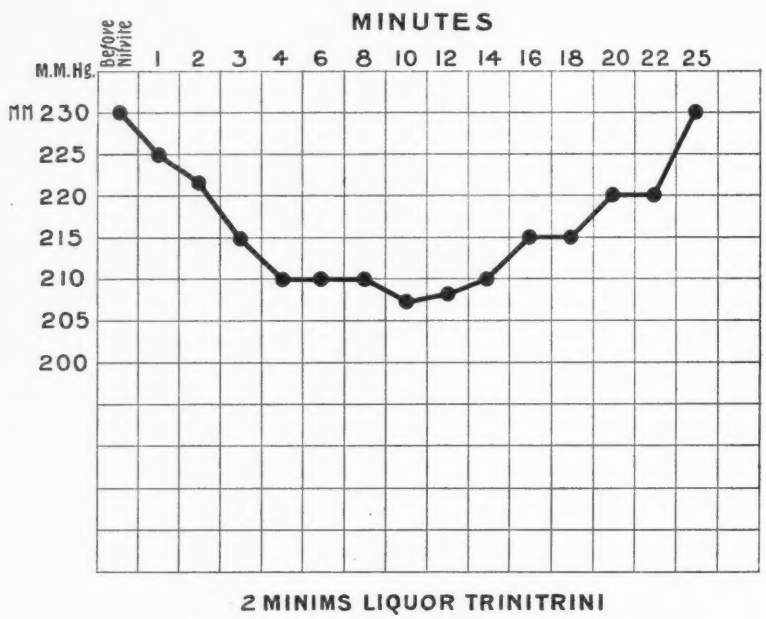



Fig. 1.

observations I found a fall in times varying from 30 to 90 seconds with an average of exactly a minute. In no case did I find the action delayed beyond 90 seconds.

2. *Amount of fall produced.* This varied from 20 to 35 mm. of mercury over the twelve observations with an average of 28 mm.

3. *Time of maximum fall.* The full effect of a single dose is produced gradually, though within a short space of time. The times varied from 3 to 8 minutes with an average of 5 minutes.

4. *Time during which the pressure remains at its lowest.* With liquor trinitrini the blood pressure is maintained at its reduced level for only a short time, varying from 2 to 5 minutes. After this the pressure begins to rise.

5. *Time after which the pressure reaches its original level.* When the pressure begins to rise again and the effect of the nitrite to pass off, the return to the original level is gradual, but much slower than the fall. In my observations the original level was reached in times varying from 20 to 28 minutes after the drug had been administered. The time was delayed to the latter figure in only one case.

Summarizing the action of a single dose of liquor trinitrini we have:— (1) The vaso-dilator effect follows within a minute after administration. (2) The reduction in pressure amounts to between 25 and 30 mm. of Hg. (3) The maximum effect is produced in 5 minutes. (4) This maximum effect is main-

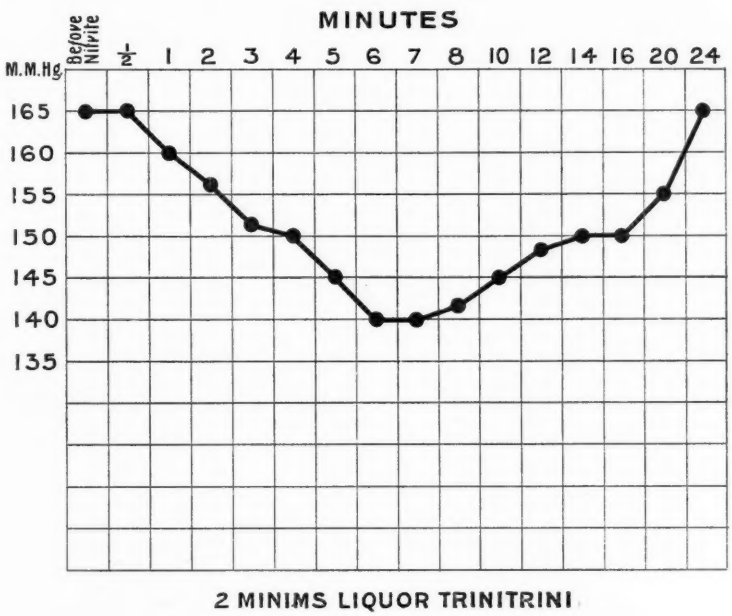



FIG. 2.

tained for 2 minutes. The pressure then begins to rise again and reaches its original level in 28 minutes or, say, half an hour.

In my observations there were instances in which no or little fall of pressure was obtained with liquor trinitrini. This I found with the other nitrites. They could be definitely grouped, and I will refer to them later.

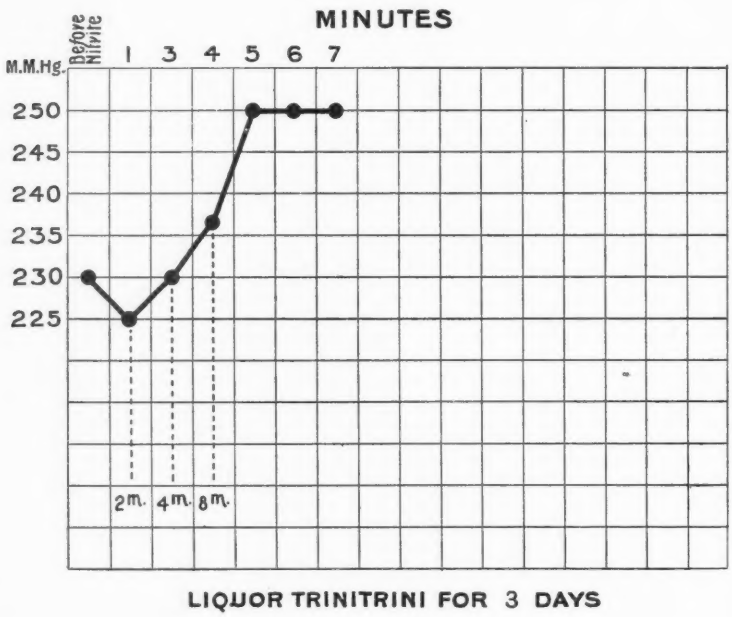
### *Effect of Repeated Doses.*

In suitable cases that had acted to a single dose, I made observations with liquor trinitrini given three or four times a day and in increasing doses, as

I wished to ascertain if by it one might be able to maintain a reduction in blood pressure.

I did not observe this in any case. But when one considers that the effect of a single dose has passed off in half an hour, a permanent reduction could not be expected. Even by giving the drug very frequently and in increasing doses this is not attained.

The medicinal dose of liquor trinitrini is set down as 1 or 2 minims. This I found could be very readily and quickly increased. A tolerance to the drug soon becomes established, and quantities up to 60 minims in the twenty-four hours are readily borne. With the increased doses, however, I did not observe




LIQUOR TRINITRINI FOR 3 DAYS

FIG. 3.

corresponding effects on the blood pressure, either as regards length of time of action or amount of fall in pressure.

In certain conditions of hypertension, liquor trinitrini (and the other nitrites also) produces little or no vaso-dilator effect, and in these cases the drug, especially if pushed to any extent, may even do harm.

One such case I should like to refer to here.

In a patient suffering from advanced chronic Bright's disease I had failed to obtain a vaso-dilator action with 2, 3, and 4 minims of liquor trinitrini on successive days. The patient was then put on 2 minims thrice daily, which was gradually increased until on the fifth day he was taking 8 minims. The nitrite was stopped on the seventh day, and the above chart shows the effect on the

blood pressure. At the end of the first day the pressure had fallen a little—5 mm. of Hg. With the increase of the nitrite the pressure, instead of falling, gradually rose, and by the seventh day had risen to 250 mm. Concomitantly with the rise in pressure the patient had unpleasant symptoms. On the fifth day he complained of violent occipital headache, pulsating in character. On the sixth day he became short of breath and was unable to lie down, and became sleepless. No change took place in the amount of urine passed. On the seventh and eighth days a haemothorax developed, and on the latter 32 oz. of deeply blood-stained fluid was drawn off the left side of the thorax, and on the tenth day 40 oz. of similar fluid from the right side of the chest. After the

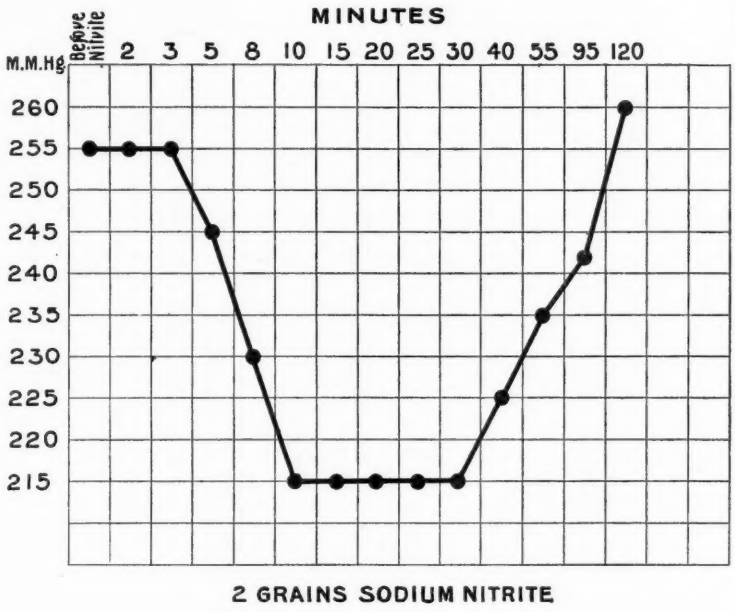



FIG. 4.

nitrite had been stopped and the fluid drawn off, the symptoms gradually subsided.

Subsequently in similar cases I observed the same tendency with continued and increasing doses of liquor trinitrini. Headache set in after a few days, followed by shortness of breath. The symptoms disappeared in every case with the cessation of the nitrite.

## II. OBSERVATIONS WITH SODIUM AND POTASSIUM NITRITES.

These were made with freshly-prepared solutions of the drugs, which were administered under the same conditions as liquor trinitrini.

Some of the observations were made in the same cases as liquor trinitrini in order to obtain a comparison between the various nitrites—others in different hypertension cases.

As might be expected, I could detect no difference in their action between sodium and potassium nitrites—both acted equally well.

Twenty observations were made in all.

The analysis will be followed under the same headings as liquor trinitrini.

The two accompanying charts (Figs. 4 and 5) will give an idea of their action in suitable cases in doses of 2 and 3 grains.

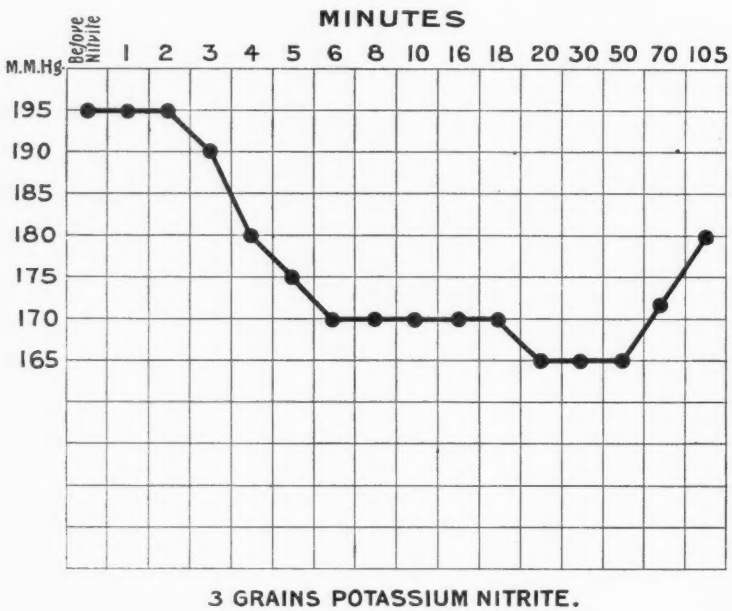



FIG. 5.

1. *Time in which the pressure begins to fall.* In more than the twenty observations the time varied from 2 to 7 minutes, with an average of 4 minutes.

2. *Amount of fall produced.* In more than the twenty observations the amount of fall varied from 20 to 50 mm. of Hg with an average of 32·5 mm. This amount is about 20 per cent. more than with liquor trinitrini and about represents the figure I obtained when the two drugs were afterwards used in the same case.

3. *Time of maximum fall.* This varied from 8 to 40 minutes (the latter only in one case) with an average of 15·4 minutes. The fall is a gradual one during the 15 minutes, amounting to about 5 mm. of Hg every 2 minutes until the full effect is produced.

4. *Time during which the pressure remains at its lowest.* With sodium and potassium nitrites in over the twenty observations this varied from 16 to 65 minutes.

5. *Time after which the pressure reaches its original level.* The rise in pressure is very gradual and much slower than the fall. The original level of pressure is reached in times varying from 60 to 120 minutes or slightly over.

Summarizing the action of sodium or potassium nitrite in a single therapeutic dose, we have:—(1) The vaso-dilator effect is produced in 5 minutes. (2) The blood pressure falls about 32 mm. (3) The maximum effect is produced in 15 minutes. (4) This maximum fall is maintained for from 20 to 60 minutes. (5) The original pressure is reached in from over 1 hour to over 2 hours.

### *Effect of Repeated Doses.*

As these drugs act in a therapeutic dose for about two hours there will be a greater expectation of maintaining a reduction in pressure with repeated doses. Several of these cases that responded well to a single dose I put on the nitrite three times a day, with sodium and potassium nitrites. I did not find any tendency to a tolerance being established. For periods of a fortnight and over one was able to maintain a reduction in pressure, not constantly at the lowest level of a single dose, but still quite marked. The effect passed off very quickly after the drug was stopped, and the pressure within twenty-four hours reached its original level.

### *Dosage employed.*

These observations were made entirely with doses of 2 and 3 grains. Previously I had made several with smaller doses of ½ grain, but the effect was slight and I adopted 2 and 3 grain doses for reasons I will afterwards detail. Two grain doses are usually sufficient, for I was unable to discriminate between the effects of 2 and 3 grain doses given in the same cases.

## III. Observations with Erythrol Tetranitrate.

I made first of all seven observations with fresh Burroughs, Wellcome & Co.'s tabloids in doses of ½ and 1 grain.

| | | | | | | |
|---|---|---|---|---|---|---|
| Observation | 1, | dose | 1 gr. | No change in pressure in | | 3½ hours. |
| „ | 2, | „ | 1 gr. | „ | „ | „ 25 minutes. |
| „ | 3, | „ | 1 gr. | „ | „ | „ 1 hour 40 minutes. |
| „ | 4, | „ | 1 gr. | „ | „ | „ 1 hour 10 minutes. |
| „ | 5, | „ | ½ gr. | „ | „ | „ 36 minutes. |
| „ | 6, | „ | ½ gr. | „ | „ | „ 1 hour 25 minutes. |
| „ | 7, | „ | ½ gr. | „ | „ | „ 1 hour 40 minutes. |

These observations were made in the same patients in whom subsequently I obtained a positive result with another preparation of the drug.

*Observations with Martindale's Chocolate Tablets.*

I made fourteen observations in all.

The accompanying charts (Figs. 6 and 7) readily show the action in two cases.

*Analysis of its Action.*

1. *Time in which the pressure begins to fall.* In more than fourteen observations the pressure began to fall in times varying from 4 to 8 minutes, with an average of nearly 6 minutes. Following the initial reduction the fall is one of about 5 mm. of Hg every 2 minutes until a maximum is reached.

2. *Amount of fall produced.* The fall in pressure varied from 20 to 50 mm. of Hg, with an average of 34 mm. (There is no relationship between the height of the original pressure and the amount of fall.)

3. *Time in which a maximum fall is reached.* This varied from 14 to 40 minutes, with an average of slightly over 22 minutes. I may point out here that such an early fall in pressure after the administration of erythrol tetranitrite and a maximum reached in 22 minutes is not what is generally supposed to be the case. Bradbury, in his original observations with this drug, describes the fall as setting in slowly and only very gradually reaching a maximum. In one instance the pressure fell only 22 mm. of Hg in 28 minutes, and it was only after 2 hours 48 minutes that the lowest level was reached—a fall of 40 mm.

His observations were made with the sphygmograph, but in my haemomanometric observations I never failed, in cases that responded to erythrol, to obtain a much speedier initial fall and maximum effect.

4. *Time during which the pressure remains at its lowest.* A maximum effect is produced in a little over 20 minutes, and this maximum is maintained for periods varying from 60 to 120 minutes, with an average nearer the two hours than the one, and it is only after between one and a half to two hours that the pressure again begins to rise.

5. *Time in which the original pressure is again reached.* The pressure begins to rise in about two hours, and the return to normal is very slow. Owing to the exigencies of the ward it was difficult in all the cases to make observations until the action had completely passed off, but in my observations I found the following :—

| | | | | | | |
|---|---|---|---|---|---|---|
| Observation | 1, | observed for | 60 | minutes. | Pressure still at its lowest level. |
| „ | 2, | „ | 70 | „ | „ | had just begun to rise. |
| „ | 3, | „ | 115 | „ | „ | had risen 5 mm. from lowest. |
| „ | 4, | „ | 115 | „ | „ | had risen 10 mm. from lowest. |
| „ | 5, | „ | 90 | „ | „ | still 15 mm. below original. |
| „ | 6, | „ | 480 | „ | „ | still 20 mm. below original. |
| „ | 7, | „ | 240 | „ | „ | still 15 mm. below original. |
| „ | 8, | „ | 480 | „ | „ | still 15 mm. below original. |
| „ | 9, | „ | 480 | „ | „ | still 5 mm. above original. |
| „ | 10, | „ | 180 | „ | „ | still 30 mm. below original. |

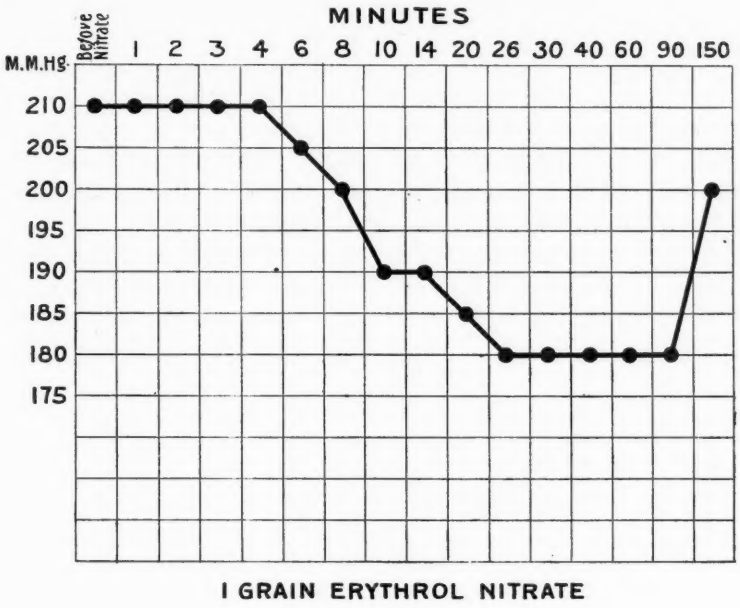

MINUTES
Before Nitrate
1 2 3 4 6 8 10 14 20 26 30 40 60 90 150
M.M.Hg.
210
205
200
195
190
185
180
175
1 GRAIN ERYTHROL NITRATE

Fig. 6.

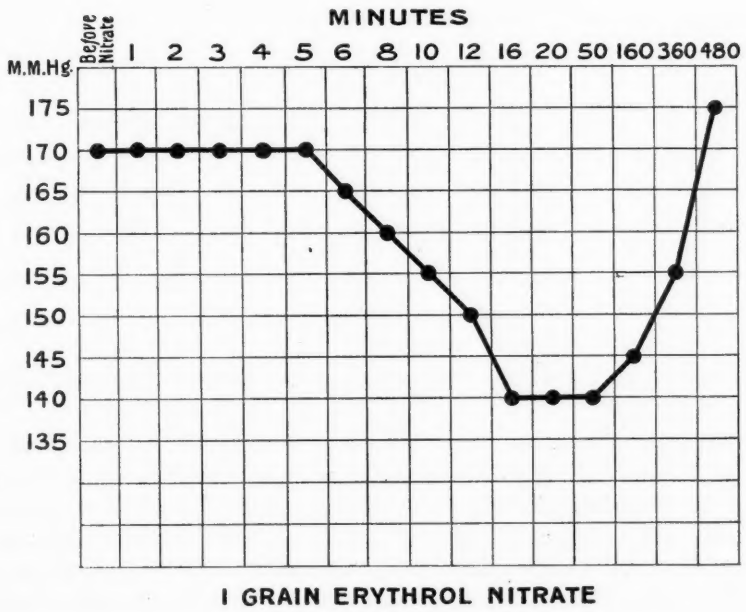

MINUTES
Before Nitrate
1 2 3 4 5 6 8 10 12 16 20 50 160 360 480
M.M.Hg.
175
170
165
160
155
150
145
140
135
1 GRAIN ERYTHROL NITRATE

Fig. 7.

From these figures it will be observed that in some cases even after 4, 5, and 6 hours the effect of erythrol has not passed off.

Summarizing these results with erythrol nitrate we have: (1) The vaso-dilator action is evident in about 5 minutes. (2) The fall in pressure is gradual, and the amount of reduction is about 35 mm. of Hg. (3) The maximum effect is produced in about 22 minutes. (4) The maximum reduction is maintained for about 2 hours, the rise towards the original level is very gradual, and the complete effect passes off in from 5 to 6 hours.

My observations were made with $\frac{1}{2}$-grain and 1-grain tablets. Between them in the same cases I was not able to observe a definite relationship. The

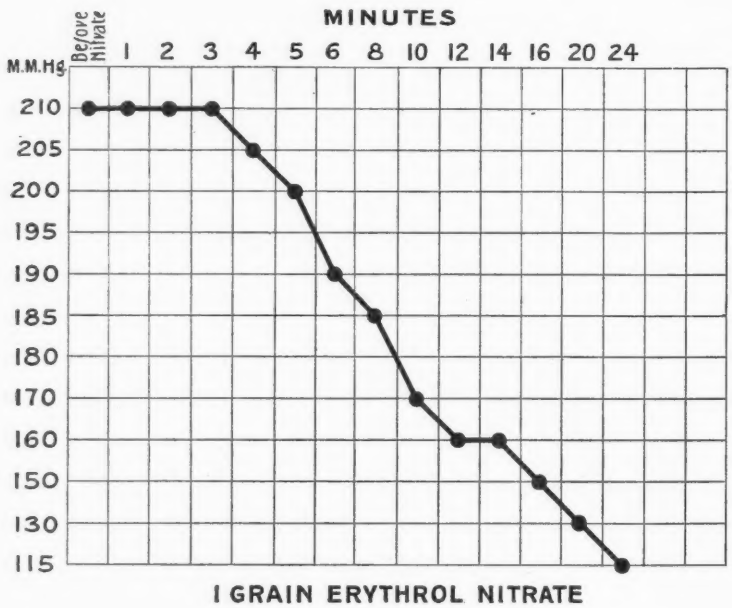



FIG. 8.

larger dose certainly did not produce double the amount of fall, nor did the effect last twice as long.

With erythrol tetranitrate I did not observe any tendency to the establishment of a tolerance. The drug is not so well borne as liquor trinitrini and sodium or potassium nitrites. In a number of cases there is a marked susceptibility to the drug, and in several instances symptoms of over-action manifested themselves. One in particular was most marked, and it is worth recording. The patient suffered from granular kidney in its earlier stages, with a persistent high pressure of about 220 mm. of Hg, with a tendency to periodic

rises to 250 mm. To liquor trinitrini and sodium nitrite he readily responded. On the day of observation with erythrol the pressure was 210 mm. One grain was given. He reacted very readily, as the chart (Fig. 8) will show.

The pressure began to fall in 4 minutes and thereafter fell about 5 mm. every 2 minutes. When the pressure had fallen to 170 mm.—in 10 minutes—he began to have unpleasant symptoms. He became pale, cold sweat broke out on him, he complained of feeling giddy, sick and faint. His pulse became slower. The pressure continued to fall steadily, the symptoms became aggravated, and at the end of 25 minutes he fainted in bed. The last estimation of the pressure I was able to make was at the end of 24 minutes. It was then 115 mm.

In this case the 1 grain of erythrol had produced too great an action. The patient had bled into his abdominal veins. It was evening of the same day before he rallied, and even then his pressure was very considerably below his normal level.

*Erythrol in continued doses.* Erythrol in a single dose produces an action lasting about six hours. It is reasonable to expect that if given three times a day one would be able to maintain a reduction in pressure. This I have obtained in many suitable cases.

It is not necessary to detail the cases, but so long as the drug is administered in a dose of ½ grain or of 1 grain a reduction of about 30 mm. of Hg can be maintained in cases that react to a single dose.

## IV. Observations with Mannitol Nitrate.

I made eight observations in all, with Martindale's chocolate tablets in 1-grain doses. The two charts (Figs. 9 and 10) show its general action.

### *Analysis of its Action.*

1. *Time in which the pressure begins to fall.* The initial fall begins in times varying from 8 to 16 minutes, with an average of 12 minutes.

2. *Amount of fall produced.* This varied from 25 to 50 mm., with an average of about 35 mm.

3. *Time in which the maximum is reached.* This varied from 60 to 120 minutes. With mannitol I found the fall more gradual than with the other nitrites. In several instances I made observations in the same cases with erythrol and mannitol and always found the full effect produced much more quickly with erythrol than with mannitol.

4. *Time in which the pressure begins to rise.* This varied from 2½ to 3 hours. After this the pressure rises slowly.

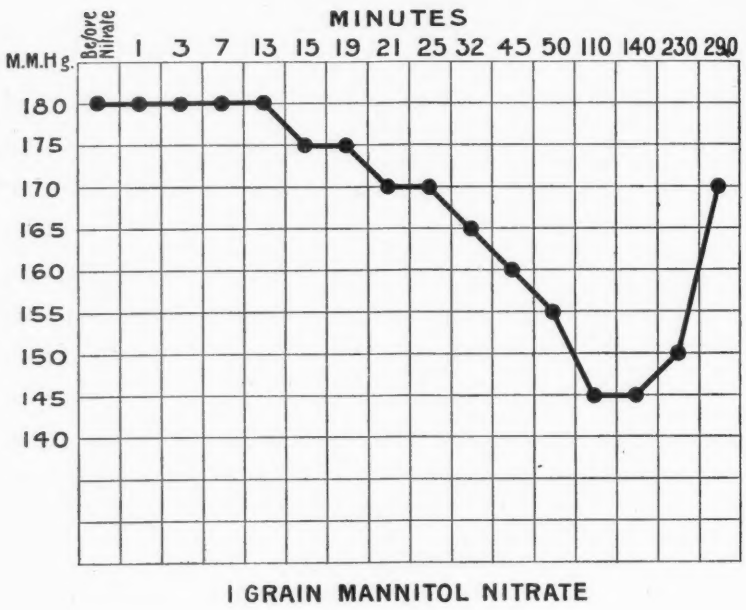

MINUTES
Before Nitrate
1 3 7 13 15 19 21 25 32 45 50 110 140 230 290
M.M.Hg.
180
175
170
165
160
155
150
145
140
1 GRAIN MANNITOL NITRATE

FIG. 9.

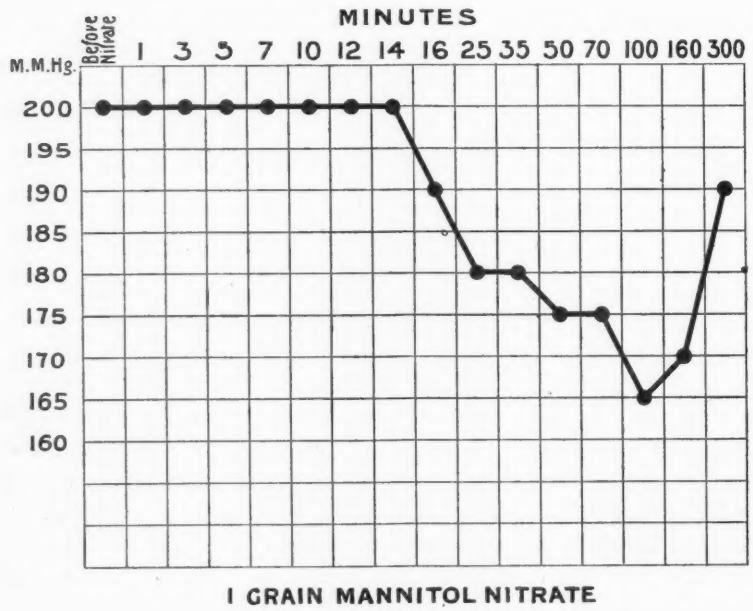

MINUTES
Before Nitrate
1 3 5 7 10 12 14 16 25 35 50 70 100 160 300
M.M.Hg.
200
195
190
185
180
175
170
165
160
1 GRAIN MANNITOL NITRATE

FIG. 10.

5. *Time in which the original level of pressure is reached.*

Observation 1. At end of 3 hours had just begun to rise and in 6½ hours it was 5 mm. above original pressure.

„ 2. In 3 hours pressure still 25 mm. below original.

„ 3. „ 4½ „ „ „ 5 mm. „

„ 4. „ 4½ „ „ „ 25 mm. „

„ 5. „ 6 „ „ „ 10 mm. „

„ 6. „ 5 „ „ „ 10 mm. „

„ 7. „ 3 „ „ „ 10 mm. above original.

Summarizing the action of mannitol hexanitrate:—(1) Mannitol produces an action in 15 minutes. (2) Mannitol produces a fall of about 35 mm. (3) The maximum effect is produced in 2½ to 3 hours. (4) The pressure begins to rise again after 3 hours and the original level of pressure is again reached in about 6 hours.

The effect of continued doses is the same as with erythrol tetranitrate. Examples need not be detailed. A reduction of pressure of about 30 mm. can be maintained in suitable cases so long as the drug is being administered. The pressure rises again within 24 hours.

## V. Cobalto-nitrite of Potassium.

This nitrite has been employed chiefly in America. It is a more stable compound than potassium nitrite and is less rapidly broken up in the system, and it was thought a more prolonged action would result from its administration. For observations with it I chose cases that had already been tested with liquor trinitrini and potassium nitrite.

The results were negative. Up to 70 minutes I obtained no vaso-dilator effect in six cases.

## Conclusions.

From these observations certain conclusions can be drawn as to the individual and relative action of nitrites and organic nitrates.

1. *Action of nitrites generally.*

(*a*) Nitro-glycerine or liquor trinitrini, sodium nitrite, potassium nitrite, erythrol tetranitrate, and mannitol hexanitrate are all powerful vaso-dilators. With cobalto-nitrite of potassium I did not find a vaso-dilator action.

(*b*) Their action can be definitely ascertained as regards the time of initiation, amount of fall produced, and length of time the action lasts.

(*c*) These nitrites produce a fall in pressure only in certain cases of hypertension. In others they produce no action.

2. *Comparative action of the various nitrites.*

These nitrites are all powerful vaso-dilators in suitable cases, but well-defined differences exist among them.

(*a*) Time in which the pressure begins to fall.

The order of their action is the order in which I have described them.

(i) Nitro-glycerine or liquor trinitrini—1 minute.
(ii) Sodium and potassium nitrites—5 minutes.
(iii) Erythrol nitrate—about $5\frac{1}{2}$ minutes.
(iv) Mannitol nitrate—about 12 minutes.

(*b*) Amount of fall in pressure in millimetres of mercury.

The average amounts were :—

(i) Liquor trinitrini—28 mm.
(ii) Sodium and potassium nitrites—32 mm.
(iii) Erythrol nitrate—35 mm.
(iv) Mannitol nitrate—35 mm.

Between the least and the greatest there is only a difference of 6 mm.—a figure that might be reduced over more extensive observations.

(*c*) Time in which the maximum fall is reached.

In the four nitrites the average time was :—

(i) Liquor trinitrini—$4\frac{1}{2}$ minutes.
(ii) Sodium and potassium nitrites—14 minutes.
(iii) Erythrol tetranitrate—22 minutes.
(iv) Mannitol hexanitrate—about 100 minutes.

These nitrites begin to act in 1, 5, $5\frac{1}{2}$, and 10 minutes respectively; the maximum therefore is produced in $3\frac{1}{2}$, 9, $16\frac{1}{2}$, and 90 minutes after the vaso-dilator action begins. The amount of fall produced by each is about the same, and therefore with liquor trinitrini there is a very sudden and prompt action, not so sudden in the cases of sodium and potassium nitrites, more prolonged with erythrol nitrate, and lastly, a very gradual and slow action with mannitol nitrate.

(*d*) The rise in pressure after the fall.

Variation in action between the different nitrites becomes still more evident when one studies the rise in pressure towards its original level.

1. With *liquor trinitrini* the pressure begins again to rise almost immediately a maximum fall has been reached. The rise is slower than the fall, but in all cases the effect of the drug has completely passed off in 30 minutes.

2. *Sodium and potassium nitrites* have a more extended action. A maximum fall is reached in about 10 minutes after the initial action has set in. This is maintained for from 40 to 50 minutes. The rise then is slow and the effect does not pass off until 2 hours have passed after the administration.

3. *Erythrol* and *mannitol* behave alike as regards length of action. The maximum effect is maintained for between 1 and 2 hours. The rise is very gradual, and the original level is reached only after 5 or 6 hours from the time of administration.

The various points determined for these nitrites in these observations may be seen from the following diagram (after Bradbury).

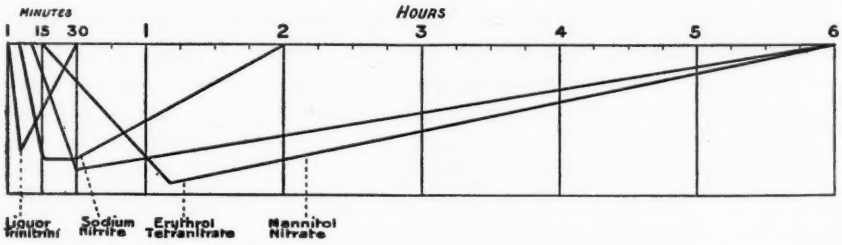



FIG. 11.

In my observations with all the nitrites I found that in certain cases they produced little or no vaso-dilator action. In some a reduction was obtained of from 5 to 10 mm. in the usual time for the particular nitrite. In others no reduction was obtained after observation over the usual time of action. A rise in blood pressure occurs in certain well-defined clinical conditions. In chronic inflammatory Bright's disease and in chronic Bright's disease the pressure is markedly raised, the rise being progressive. In generalized arterio-sclerosis a progressive increase in blood pressure is usually found.

These clinical conditions in their earlier stages I invariably found responded to the nitrites, as I have indicated, but ultimately a stage is reached, seen most particularly in advanced chronic Bright's disease when the nitrites produce little or no response. The reasons for this I may discuss in a future paper.

In heart and kidney cases too, where the blood pressure is raised, and where in addition marked oedema is present, nitrites do not act well. After the oedema has disappeared the usual vaso-dilator action may reappear.

### *Dosage of the Therapeutic Nitrites.*

It has to be recognized that, in all cases, though within limits, high pressure is not necessarily harmful to the individual, and the idea that it has always to be attacked by every means in our power in order to obtain again a normal level has just sufficient truth to be a serious misconception. In individuals in whom it is found, it is to be looked on primarily as a compensatory change. Just as a left ventricle in aortic incompetence has to hypertrophy to accommodate itself to the altered conditions due to the aortic leak, so probably high blood pressure must be considered compensatory if the proper relationship is to be maintained between the various parts of the circulation and between the circulation and the tissues. Undoubtedly we find, in every case that is followed for some time, that once started the tendency is for the blood pressure to increase progressively, and our aim is to prevent this increase being too sudden and exaggerated. That too great a reduction may be harmful I have indicated in a detailed case with erythrol, where unpleasant symptoms were

induced by too large a reduction. They set in too at a point in the pressure too high for a normal standard, but too low for the particular individual's vascular economy.

From the observations I have detailed and many others, I made an attempt to ascertain what reduction of pressure is both necessary and safe for relieving and alleviating symptoms and in maintaining the pressure at a level that shall be least innocuous to the patient. I made observations in many cases with hypertension when symptoms had developed, such as pain, headache, giddiness, epistaxis, conditions of stomach, &c., that could be traced to the elevated pressure.

From my observations with nitrites in varying doses I invariably found that such symptoms were alleviated or disappeared altogether with a reduction of pressure amounting to about 30 mm. of Hg, and if this fall could be maintained the symptoms did not reappear and the individual's general condition improved. I then made observations with the active nitrites in varying amounts to ascertain the quantity of each that would produce as nearly as possible such a reduction. It was after and on account of these investigations that I adopted the doses employed in the foregoing observations with the various nitrites.

1. *Liquor trinitrini.* Where a single dose—to be repeated if necessary in half an hour—is prescribed, I would recommend 2 minims as one most likely to obtain the desired effect.

2. *Sodium and potassium nitrites.* In suitable nitrite cases 2 grains produces a reduction of just over 30 mm. of Hg. This action will last 2 hours, and only after this is it necessary to repeat it. No benefit is obtained by increasing the dose and a less dose will not give the desired effect.

3. *Erythrol nitrate.* With this drug a dose of ½ to 1 grain will produce the beneficial reduction, and the effect will last about 6 hours. Owing to individual susceptibility to erythrol, and in some cases having obtained sufficient reduction with the smaller dose, I would recommend that it be used in all cases to start with.

4. *Mannitol nitrate.* I have used only tablets of 1 grain. These produce the necessary reduction of pressure and effects.

With it I have not observed the same individual susceptibility or any tendency to unpleasant effects, probably owing to the fact that it produces its maximum effect much more slowly than erythrol.

I would point out that, in all cases, the useful and suitable dose of a nitrite for each individual can readily be ascertained by making an observation or two and noting the effect of the nitrite as to the amount of fall produced and time the action lasts.

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Hay, *Practitioner*, Lond., 1860, xxx. 321.
Leech, *Brit. Med. Jour.*, 1893, ii. 6.

# FURTHER RESEARCHES ON THE ETIOLOGY OF ENDEMIC GOITRE[1]

By ROBERT McCARRISON

With Plates 14–16

## Object of the Research.

My previous investigations on this subject led me to the conclusion that endemic goitre was due to no dissolved ingredient of goitre-producing waters, but that in all probability the active principle in the production of the disease existed in suspension in such waters (1), (2). It has been the object of the present research to test, by means of experiments on man, the truth or otherwise of this view, and to determine, as far as possible, the nature of the suspended ingredient which I had surmised to be responsible for the production of the disease. The experimental and other investigations which I have carried out may be summarized as follows :—

I. The experimental administration to man of suspended matter, separated by filtration from goitre-producing waters.

II. The experimental administration to man of *boiled* suspended matter, separated by filtration from goitre-producing waters.

III. The administration to goitrous individuals of intestinal antiseptics, notably thymol.

IV. Experiments on monkeys to test the possibility of the spread of the disease by the faeces of sufferers from it.

V. The microscopical examination of the faeces of goitrous individuals.

The observations to be recorded have been made in Gilgit (Kashmir) and refer only to goitre as it occurs there.

## I. The Experimental Administration to Man of Suspended Matter, separated by Filtration from Goitre-producing Waters.

*Experiment* A.—*Carried out March to May,* 1906.

Six healthy young men, aged between 18 and 20 years, volunteered for this experiment. Of these, two—Davia and Karim—had lived in Gilgit before, and

[1] A summary of this paper was read before the Royal Society on Nov. 26, 1908.

both had then suffered from slight enlargements of the thyroid gland. These enlargements had disappeared on the men leaving the district, with the exception of a small nodule which still remained in the isthmus of Davia's thyroid (Fig. 1). Both these men had arrived on their second visit to Gilgit six months prior to the date on which the present experiment was commenced; the thyroid gland had undergone no change in either during this period. It was thought that they were likely to prove more susceptible to goitrous influences than men who had not previously suffered from the disease. The other four men, who were new-comers to the district, were in all respects perfectly normal. All six were kept under the closest observation for some time prior to the commencement of the experiment, and during this time the same precautions were taken to guard against goitrous infection from outside sources as were employed during the course of the experiment. The experiment commenced on March 15, none of the subjects having shown any signs of enlargement of the thyroid during the preparatory period of observation.

During the whole course of the experiment the six individuals lived under the strictest guard; they were well fed, their diet being chiefly vegetable, and their hygienic conditions of life were excellent. They did no work, and were not permitted to handle the soil. They lived on a non-goitrous site near the village of Barmis. They were provided with water, for drinking, bathing, and other cleansing purposes, from the Barmis spring, which is non-goitre producing, but which, as an added precaution, was boiled. In no case was the restraint imposed upon them broken through.

Water, purposely made muddy by agitation while flowing through its channel, was brought daily from the village of Kashrote, where goitre prevails to the extent of 45 per cent. of the total population. It was filtered in large quantities through a Berkfelt house filter. The deposit on the candle was washed off in distilled water, and a quantity of the dark grey mixture, equal to about four ounces, was given to each subject in milk every morning before the first meal of the day.

No noticeable change was observed to have occurred in any case until March 28, thirteen days after the experiment began. On this date Davia, who, it will be remembered, had suffered from goitre on a former occasion, showed an evident swelling of the whole thyroid gland. There was considerable pulsation in the neck, and the left lobe was slightly more enlarged than the right. He affirmed that he became aware of the swelling suddenly. The thyroid glands of the other five cases were apparently unaltered.

March 30. The pulsation in Davia's neck was not so evident, and the gland was obviously smaller than it had been two days before.

The second man, Karim, who had also suffered from goitre on a former occasion, complained of a sense of fullness in the throat; there was considerable pulsation, and the gland was readily palpable on the left side though not visibly enlarged. The other four cases showed no change.

April 1. Davia. The thyroid gland was again larger, as on March 28, and there was marked throbbing in the neck.

Karim. There was considerable throbbing about the gland region, but it was not noticeably altered in size since March 30.

There was some pulsation in the neck in two other cases, but it was not marked.

April 6. Davia. The gland had increased considerably in size, and was fuller on the left than on the right side. He affirmed that 'it was sometimes larger, sometimes smaller'.

Karim. There was a fullness of the neck noticeable, especially on the left side, where there was slight bulging of the sterno-mastoid. Pulsation was also more marked on this side. On manual examination the gland was noted to be enlarged on the left side, less so on the right.

In two other cases the pulsation in the neck was still present, but was not marked. The other cases were unaltered.

April 8. Davia. The neck was more swollen than at any time during the course of the experiment. He was accordingly photographed (Fig. 2). The photograph shows very clearly the extent of the goitrous enlargement. There was no further alteration in any of the other cases.

April 10. There was no apparent change in Davia's or Karim's case. The pulsation in the neck of two other cases appeared slightly more marked, though no enlargement of the thyroid could be detected by manual examination.

April 13. The goitre in Davia's case appeared to be slightly smaller. There was no apparent change in any of the other cases.

April 16. Davia's goitre was undoubtedly slightly smaller. In Karim's case the gland had not enlarged further. There was no change in the other cases.

The experiment was continued in the case of Davia till April 25; the gland was then smaller than it had been on April 8. He was subsequently cured by means of thymol.

In the case of Karim the experiment was continued until May 8. No further increase in size took place, nor did any diminution occur. The circumference of the neck had increased in this case $1\frac{1}{2}$ cm.

In the other four cases the experiment terminated on the fifty-third day without any appreciable swelling of the gland having taken place, though the pulsation in the necks of two of these may have been the evidence of an increased functional activity of the organ.

*Experiment* B.—*October and November*, 1907.

I was myself the subject of this experiment. I had resided in a goitrous locality for five years prior to the date of the experiment without having ever shown signs of enlargement of the thyroid gland. The European and better-class residents of Gilgit use the water of the Barmis spring, which is notorious as a non-goitre-producing water and is of exceptionally pure quality. My house, also, was situated in the village of Barmis, where goitre does not occur.

There was no possibility of my being able to acquire the disease from other sources.

The experiment commenced on October 15. I consumed every morning before breakfast half a tumblerful of the Kashrote water suspended matter, prepared in the same way as in the preceding experiment. I was at the time taking hard exercise, and my neck measured 40 cm. (Fig. 3). No change was observed until October 30, when I noticed that my collar felt uncomfortably tight. On examination the thyroid gland was found to be uniformly enlarged, but more markedly so on the right side. The circumference of my neck was 42 cm. I had noticed that my bowels had been loose during the fifteen days the experiment had lasted, possibly owing to the quantity of muddy water I was consuming every morning.

The experiment was continued until November 9, and during these ten days the gland fluctuated in size considerably; at one time I was hardly aware of its existence, while at another, and especially at night, it was a cause of discomfort. Fig. 4 shows the appearance on November 9, when the swelling was slightly greater than on October 30. The average of several measurements made by my assistant was 42½ cm. There was a noticeable bulging of the right sterno-mastoid, while the isthmus of the gland could be felt and seen as a rounded prominence over the trachea. On performing the act of swallowing in front of a mirror I was able to see very clearly the extent of the enlargement. The experiment was discontinued after this date, and the swelling had completely disappeared eight weeks later, aided in its disappearance by small doses of thyroid extract, which, however, I used only for the first three weeks.

*Experiment* C.—*February and March*, 1908.

The experiment as detailed in A was repeated in the case of six young men in all of whom the thyroid gland was perfectly normal. The duration of the experiment was one month. The results were as follows:—In one case the circumference of the neck increased from 34½ to 36 cm. Figs. 5 and 6 show the appearances presented before and after experiment. There was a slight bulging of both sterno-mastoids, and the gland was readily palpable. The result in this case was similar to that in the case of Karim (Experiment A), though perhaps slightly less marked.

In another case the circumference of the neck increased 1½ cm., but in other respects the reaction was slight.

In a third the man was conscious of a sense of 'fullness of the throat' at times; there was an increase of one centimetre in the circumference of the neck, and throbbing was from time to time observed. In these cases the swelling made its appearance gradually. There was no reaction in the other three cases.

### II. The Experimental Administration to Man of *Boiled* Suspended Matter, separated by Filtration from Goitre-producing Waters.

Matter in suspension in the waters of Gilgit is largely made up of mineral matter in a fine state of division. The view is held by some that it is to this finely divided mineral matter that goitre is due. It was determined, therefore, to subject the matter in suspension, separated by filtration from goitre-producing waters, to prolonged boiling. This treatment leaves the mineral part more or less unaltered while it destroys the living ingredients. The muddy water was accordingly filtered and the residue washed off in distilled water in the same way as described in Experiment A. These washings were then boiled for ten minutes, allowed to cool, and administered to the subjects in the same way as in the foregoing experiments.

#### *Experiment* D.—*February and March*, 1908.

The enlargement of my own thyroid gland, produced as described in Experiment B, having completely disappeared, I commenced, with my servant who also volunteered for the experiment, on February 15, to consume the boiled suspended matter of Kashrote water. The details of the experiment were in all respects similar to those I have already described. We drank half a tumblerful of the boiled Kashrote water residue every morning before breakfast, and continued to do so for twenty-five days. In neither of us did the thyroid gland exhibit the slightest reaction. Fig. 7 shows the appearance of my neck on the twenty-fifth day of the experiment.

#### *Experiment* E.—*February and March*, 1908.

Every detail of Experiment A was reproduced in the present instance, the only difference being that the *boiled* residue of Kashrote water was used. Six men, average age 20 years, volunteered for the experiment. Of these, two had previously suffered from goitre and been cured; one of them is described under Section III (Case LXIV, Fig. 15). It was considered that these two youths, as in the case of Davia and Karim of Experiment A, and in my own case in Experiment D, were likely to be readily influenced by such goitre-producing agencies as might exist in the boiled 'suspended matter'. The experiment was carried out at the same time as Experiment C, the one acting as a contrast to the other. It lasted one month, and the boiled residue was consumed by the subjects not only in the morning but also in the evening; that is to say, they took twice as much residue as the men in Experiment A. Neither by manual examination, measurement, nor photograph, could an increase in size of the thyroid gland be detected in any of the six individuals.

It remains to summarize the results of the experiments detailed in this and in the preceding section. It has been found:—

(1) That of thirteen individuals who consumed the untreated residue of the goitre-producing water of Kashrote, four developed a noticeable swelling of the thyroid gland, while two others showed an increase in size of the organ demonstrable by measurement and evident to the touch.

In three cases the enlargement so produced made its appearance on the thirteenth to the fifteenth day of the experiment. It was not great, nor did it appear, under the conditions of the experiment, to be progressive.

(2) That of eight individuals who consumed the *boiled* residue of the goitre-producing water of Kashrote, none developed any swelling of the thyroid gland, and this although three were individuals peculiarly likely to respond to goitrous influences.

It may, therefore, be concluded:—

(1) That goitre is due to matter in suspension in the water.

(2) That goitre is not due to the mineral but to the living part of the suspended matter, in other words, to a living organism of disease.

(3) That the incubation period of experimentally-produced goitre is thirteen to fifteen days.

The conditions of these experiments differed from those under which the inhabitants of Gilgit live in certain important respects. The men were not subjected to the debilitating influences of defective hygiene, vitiated atmosphere, imperfect dietary, endemic diseases, and the like. Nor did that potent source of infection among an agricultural community, namely, contamination of the hands and food by the soil of the infected locality, come into operation in their case. It is to the absence of such influences as these that I attribute the fact that the experimentally-produced goitres were neither large nor progressive. Under the ordinary conditions of life in Gilgit, I have seen goitres developing in fifteen days in new-comers which were larger than these I have experimentally produced. I am convinced, therefore, that there are conditions provided by a residence in a goitrous locality apart from the water-supply which are important determining factors in the production of the disease, and that in the absence of these secondary factors the organism, which is the real causal factor, is of feeble pathogenicity.

### III. Cases illustrating the Action of Intestinal Antiseptics, notably Thymol, in Goitre.

The following examples are selected from among sixty-eight cases of goitre cured by this means:—

*Case LVIII.* Uniform parenchymatous goitre of five years' standing, in a man of 30 years of age. Circumference of neck over widest part of the goitre was 42 cm. (Fig. 8). Treated by the internal administration of thymol in powder form, 10 grs. night and morning. Patient lived at his own home,

and his habits of life remained unaltered during the whole course of treatment. Diet purely vegetable with an absence of oils, alcohol, or other solvents of thymol. The man was under treatment for three and a half months. Fig. 9 shows the appearance at the end of this time. The circumference of the neck was then 36½ cm. Some nodular thickening in the isthmus and in both lobes remained, but otherwise the swelling had disappeared. No treatment other than the intestinal antiseptic was employed.

*Case LXII.* Uniform enlargement of the thyroid gland in a man aged 35 years. Said to have developed rapidly during the twenty days prior to the commencement of treatment. There was much pulsation and engorgement of the vessels in the vicinity of the gland. The circumference of the neck over the widest part of the swelling was 41½ cm. (Fig. 10). Treated with thymol, 10 grs. night and morning, in powder form. Habits of life remained unaltered during the whole course of treatment. Diet purely vegetable with an absence of solvents of thymol. Fig. 11 shows the state of the neck on the fourteenth day of treatment, when the circumferential measurement was 40 cm. All treatment was discontinued on the eighteenth day. Fig. 12 shows the appearance of the neck three weeks later, or forty days after treatment was commenced. The neck then measured, over its widest part, 38 cm. No treatment other than the intestinal antiseptic was employed.

It will be observed, in this case, that the thyroid gland went on diminishing in size after thymol was discontinued, showing that once the stimulus to the gland's hypertrophy was destroyed by the drug the organ was enabled to return gradually to its normal state.

*Case LXIV.* Uniform swelling of the thyroid gland in a boy aged 14 (Fig. 13). The swelling was of two months' standing. Treated with thymol, 10 grs. night and morning, in powder form, while he pursued his ordinary avocations. Diet purely vegetable with an absence of solvents of thymol. Fig. 14 shows the appearance of the neck on the twelfth day of treatment. The swelling had disappeared at the end of one month (Fig. 15). No treatment other than the intestinal antiseptic was employed. This boy volunteered and was one of the subjects of Experiment E.

The treatment of goitre by the intestinal antiseptic, thymol, is of interest from an experimental rather than from a therapeutical point of view. The main action of this drug is a local one in the intestine, owing to the fact that in the absence of oil, alcohol, or other of its solvents, it is very sparingly absorbed. Its curative action is very strong though not conclusive evidence that the habitat in man of the organism responsible for the production of goitre is the intestinal tract. Further evidence on this point is afforded by the differential blood counts in cases of the disease. I have found an eosinophilia of 8·9 per cent. as the average of sixty-five cases which I have examined by this method.

## IV. Experiments on Monkeys to test the Possibility of the Spread of the Disease by the Faeces of Goitrous Individuals.

*Experiment* F.—*November to January*, 1907–8.

I have previously recorded the negative results of feeding dogs on faecal contaminated food. Dogs do not appear to suffer from goitre in Gilgit, and

the results were, therefore, regarded as inconclusive. Two young monkeys were fed on milk contaminated by the faeces of patients suffering from recent goitre. All due precautions were taken to avoid possible infection from other sources. Another young monkey was kept under similar conditions of life, but fed on clean food, as a control. No effect was observed after forty-five days of the régime. The faeces of selected cases were then mixed with Kashrote soil, fresh soil and faeces being added from time to time. The milk given to the animals was contaminated by this mixture. The experiment was continued for another forty-five days, but with negative results.

I regard the results of this experiment as inconclusive for the following reasons:—(1) It was carried out in mid-winter, a time which is unfavourable to the development of goitre. (2) It is difficult to estimate the results of an experiment of this nature in animals. Small alterations in the size of the gland cannot be detected, as is possible in man owing to the aid which the observer derives from the subject's sensations and from measurement and photography.

I also adopted the procedure of injecting the faeces of goitre cases into the rectum of a young monkey, but with negative results.

### V. The Microscopical Examination of the Faeces of Goitrous Individuals.

Two classes of organisms, apart from the bacterial flora of the gut, are met with in the vast majority of all cases of goitre in Gilgit, namely:—(1) Spores. (2) Amoebae. The former are the spores of the obligate parasites of wheat, *Tilletia laevis* and *Tilletia tritici*, and as such cannot be concerned in the production of goitre. Amoebae are very plentifully met with in the faeces. I have found them in 87 out of 103 cases of goitre examined. They existed in large numbers in the majority of cases and were sparingly met with or were not found in the minority. In non-goitrous individuals living in Gilgit, amoebae were also met with, though not with such frequency as in cases of goitre; they were found in 29 cases out of 101 examined. When amoebae did occur they were not so plentiful as in cases of goitre; in a few instances, however, they were found in abundance.

These amoebae are very distinctive in their characteristics, and develop into eight-nucleated cysts which are readily recognized in the faeces. Whether or not they have any connexion with goitre it is impossible to say at present; their further study and their relationship to goitre, if any, will form the object of a future research. It is worthy of note that I found the typical eight-nucleated cysts of these amoebae in the only case of goitre outside Gilgit which I have had an opportunity to examine. The specimen was sent to me by Major Macnab, F.R.C.S., from Simla, and the case was one of a number which appeared as an epidemic in a European boys' school there.

## VI. Results of the Research.

1. Goitre can be experimentally produced in man by the administration of the matter in suspension separated by filtration from waters which are known to be goitre-producing.

2. Goitre cannot be so produced when the suspended matter is boiled.

3. The disease is due, therefore, not to the mineral but to the living component of the suspended matter, in other words, to a living organism of disease.

4. The incubation period of experimentally produced goitre is thirteen to fifteen days.

5. Goitre can be cured by the administration of intestinal antiseptics. It is probable, therefore, that the organism which is the cause of the disease is parasitic in the human intestine.

6. The faeces of most cases of goitre in Gilgit show a plentiful amoebic infection, but whether the disease is due to this infection has not been determined.

My thanks are due to Professor Minchin and to Professor Ronald Ross for their help in connexion with the examination of the faeces.

## REFERENCES.

McCarrison, 'Observations on Endemic Goitre in the Chitral and Gilgit Valleys,' *Medico-Chirurgical Trans.*, Lond., 1906, lxxxix. 437.

McCarrison, 'Further Observations on Endemic Goitre,' *Lancet*, Lond., 1906, i. 1110.

## DESCRIPTION OF FIGURES.

PLATE 14, FIG. 1. 'Davia,' referred to in Experiment A. Shows appearance of neck at the time the experiment was commenced. There was a small nodular mass in the isthmus of the thyroid gland.

FIG. 2. The same subject. Photograph taken on the 25th day of the experiment. The increase in size of the thyroid gland is well marked.

FIG. 3. Normal appearance of author's neck. Measurement 40 centimetres.

FIG. 4. Photograph of author's neck taken on the 25th day of Experiment B. There is an evident enlargement of the thyroid gland especially noticeable on the right side. Measurement $42\frac{1}{2}$ centimetres.

FIG. 5. One of the subjects of Experiment C. Normal appearance of neck. Measurement $34\frac{1}{2}$ centimetres.

PLATE 15, FIG. 6. The same subject on the 30th day of Experiment C. Measurement of neck 36 centimetres.

FIG. 7. Shows the appearance of author's neck on the 25th day of Experiment D. No enlargement of the thyroid gland took place.

FIG. 8. Case No. 58. Shows the appearance of patient's neck previous to the commencement of treatment by thymol. Measurement 42 centimetres.

FIG. 9. The same case $3\frac{1}{2}$ months later. Measurement $36\frac{1}{2}$ centimetres.

PLATE 16, FIG. 10. Case No. 62. Appearance of patient's neck prior to the commencement of treatment by thymol. Measurement $41\frac{1}{2}$ centimetres.

FIG. 11. Same case 14 days later. Measurement 40 centimetres.

FIG. 12. The same case 40 days after the commencement of treatment. Measurement 38 centimetres. Treatment was discontinued on the 18th day, the photograph having been taken 22 days later.

FIG. 13. Case No. 64. Appearance of neck prior to the commencement of treatment.

FIG. 14. The same case after 12 days' treatment by thymol.

FIG. 15. The same case at the end of one month's treatment. This patient was afterwards one of the subjects of Experiment E.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

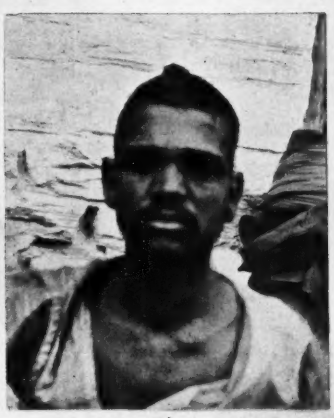


Fig. 5

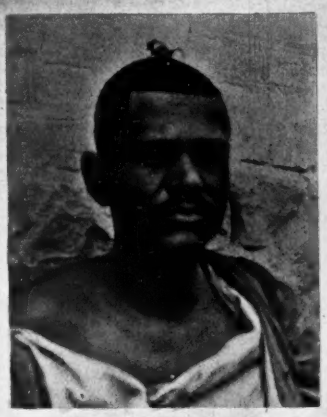


Fig. 6

Fig. 7

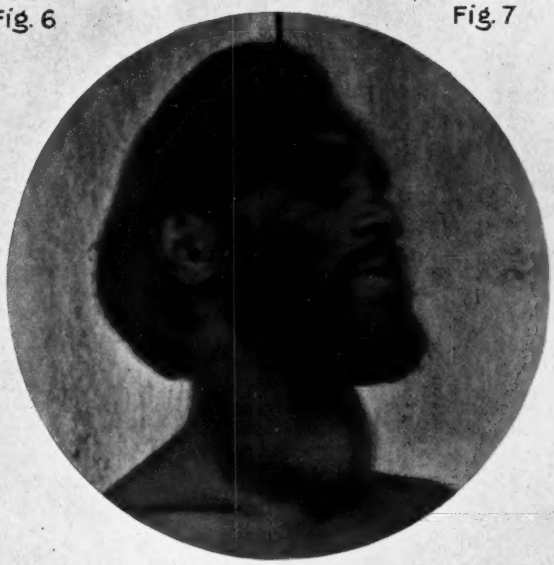


Fig. 8

Fig. 9

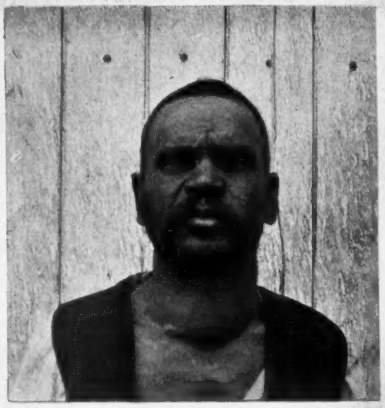


Fig. 10

Fig. 11

Fig. 12

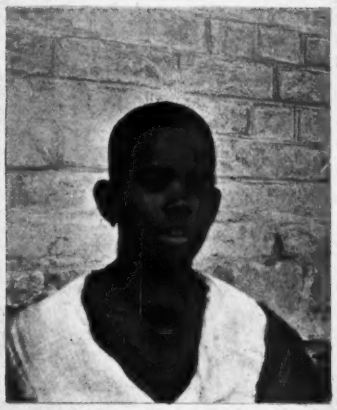


Fig. 13

Fig. 14

Fig. 15

# INFECTIVE ENDOCARDITIS

## WITH AN ANALYSIS OF 150 CASES AND WITH SPECIAL REFERENCE TO THE CHRONIC FORM OF THE DISEASE

By THOMAS J. HORDER

With Plates 17–21

i. *Introductory.* This paper is a *résumé* of many observations, clinical, pathological, and experimental, in connexion with microbic infection of the endocardium. My first intention was to concentrate my remarks upon a group of cases, possessing clinical and bacteriological features of great interest, and to the frequent occurrence of which too little attention seems to be drawn by authors. I refer to the cases of chronic infection. Whilst engaged upon an analysis of such of these cases as I have met with in private and hospital practice, Prof. Osler made a valuable contribution upon the same subject to the last meeting of the Association of Physicians, and published it in the January issue of this Journal. In various short papers published during the past eight years, dealing chiefly with the subject of blood-culture, and with the treatment of cases of septicaemia, I have drawn attention to these chronic cases of infective endocarditis and, together with Dr. Andrewes, have pointed out certain important bacteriological relations shown by them,—relations which tend to explain certain anomalies connected with them, and especially with their long duration. The appearance of Prof. Osler's lucid portrayal of the clinical picture presented by these chronic cases has stimulated me to bring together my own records of this form of the disease and, largely for the sake of comparison, to make reference to the main facts concerning the acute cases also.

The remarks which follow are based upon 150 cases, of which 115 were admitted to St. Bartholomew's Hospital, 23 to the Great Northern Hospital, and 12 were seen privately. All these cases have occurred during the past eight years.

ii. *Nomenclature.* Until the last ten years or so it was customary to distinguish two kinds of endocarditis—a 'simple' or non-infective kind, most often of rheumatic origin, and a 'fungating' or infective variety, due to one or more of the pyogenic micro-organisms. The infective form of endocarditis was also termed ulcerative, from the tendency to destructive processes associated with it; and malignant, from the very grave prognosis which its recognition entailed. Against this nomenclature various objections were raised.

[Q. J. M., April, 1909.]

Chiefly was it objected, by those authorities who came to regard acute rheumatism as itself due to a microbic infection, that on this account the term 'infective' could not logically be restricted to the second variety of endocarditis. Again, the term 'ulcerative' was by some regarded as inappropriate, because loss of tissue did not always occur in the second form of the disease, whereas it occasionally did in the first. Lastly, against the use of the term 'malignant', it was pointed out that cases of the second class sometimes recover, whilst cases of the first class sometimes die. On closer examination, neither of these criticisms of the early terms used to distinguish the forms of endocarditis appears to be very serious. Despite all the research recently undertaken by bacteriologists and epidemiologists, the proof that rheumatic fever is due to infection by a specific micro-organism is still lacking, and authorities are divided into two definite camps as regards the possibility of isolating any microbe from the blood or tissues of uncomplicated cases of this disease. The majority of observers fail to isolate any such microbe either during life or after death. Nor is this failure obviated by the use of very careful technique, the value of which can be estimated by its success in other directions. The original distinction, therefore, between non-infective and infective endocarditis may be allowed to remain, as it serves well to mark off two very different types of pathological change, leading to two very different clinical entities. The objections to the words 'ulcerative' and 'malignant' are really quite trivial, for the terms were not intended to be exactly true, but rather to indicate tendencies, which they certainly do. As, however, they are less exact than the terms non-infective and infective, and as one of them ('malignant') has another objection—that its use is confined to professional ears,—both may well be dropped. That a difference in nomenclature is necessary is obvious from the fact that every observer recognizes these two great types of endocardial disease as being different, whatever terms he may use to designate them. The assertion frequently made, that no sharp line can be drawn between the types, though true, does not dispose of the fact that in the great majority of cases the distinctions are of fundamental importance and are not difficult to recognize. Such, briefly, are the reasons for choosing the name 'infective' which heads this paper.

iii. *Frequency and importance of the disease.* During the eight years 1901–8 there were 115 patients in the medical wards of St. Bartholomew's Hospital suffering from infective endocarditis. The total number of medical in-patients during this period was 19,904. These figures yield an incidence of 1 in 173 in the wards of a large general hospital. The average number of cases treated per annum was 14·4. The disease has an importance somewhat out of proportion to its frequency, partly on account of its great gravity and partly on account of the difficulties which oft-times beset the diagnosis. It must be allowed, however, that these difficulties are not seldom the result of a lack of appreciation of the existence of the chronic cases. No adequate account of this form of the disease is to be found in the textbooks; some well-read manuals

are, indeed, altogether silent concerning it. The fulminating type of the disease is usually recognized, as also is the acute form, which lasts a few weeks at most. But the type which begins insidiously and is often chronic throughout, and of which the duration may be estimated in months rather than in days or weeks, is very apt to run a long part of its course without revealing its true nature.

iv. *Relation to Rheumatism and other diseases.* In relation to acute and subacute rheumatism, and to the endocarditis which so frequently accompanies these diseases, cases of infective endocarditis fall into three groups. Either (*a*) the patient has had rheumatic endocarditis some time previous to his present illness, or (*b*) a condition of rheumatic endocarditis has passed directly (but often imperceptibly) into that of infective endocarditis, or (*c*) there has been no rheumatism at any time. Of these groups the first is undoubtedly the commonest, and the second is the least frequent. In the majority of cases the patient is known to be suffering from, or possesses in a latent form, some valvular defect which is a sequel to rheumatic fever. Usually the interval between the occurrence of the rheumatic fever and the onset of the infective endocarditis is measured by several years, often years of good general health. When the infective stage follows directly upon a rheumatic endocarditis it seems clear that a new factor has arrived in the disease-process, comparable with the pyogenic infections (most often streptococcal) which not infrequently complicate scarlet fever, which then often constitute the condition termed 'malignant scarlet fever'. By some authorities, however, these cases are regarded as still essentially rheumatic in nature, and to them the name 'malignant rheumatism' has been applied by those who hold this view. The name is only permissible if it be understood to connote rheumatism complicated by streptococcal or other infection of the endocardium. As already mentioned, these cases are not common, particularly if due care be exercised to exclude those cases of infective endocarditis which show, at the onset, symptoms common in rheumatic fever. Of the 150 cases here collected no less than 72, or nearly one-half, gave a history of acute or subacute rheumatism, or of chorea. Next in frequency to the rheumatic group of diseases in the patients' history, but insignificant in comparison, came scarlet fever (10 cases), gonorrhoea (7 cases), typhoid fever (4 cases), malaria (4 cases), syphilis (2 cases), influenza (2 cases), Graves' disease, dysentery and pneumonia (1 case each). In 53 cases, or almost one-third of the total number, there was no history of any preceding disease. 'Athlete's heart' was known to be present in two of the cases. Of the importance of congenital heart disease special mention will be made.

v. *Relation to preceding Valvular Disease.* This is discussed under paragraph xii, p. 305, dealing with the signs of infective endocarditis.

vi. *Influence of Congenital Defects.* There seems little doubt that a congenital defect in the heart predisposes it in some measure to infection. This

predisposition is probably explained by the existence of chronic thickening of the endocardium, which is often found in connexion with these defects. Such thickening may occur in the valves when these are abnormal, such as when there are two instead of three aortic or pulmonary cusps. Or it may be found in the endocardium which surrounds a patency of the interventricular septum, or on the wall of the right ventricle opposite to the deficiency in the septum, against which the stream of blood impinges during ventricular systole. Several of the most interesting museum specimens illustrating the lesions of infective endocarditis show one or more congenital defects. In the museum at St. Bartholomew's Hospital two aortic cusps are seen in specimens 1299 g and 1301 a, and two pulmonary cusps are seen in specimen 1317. This particular defect was present in the first case of influenzal endocarditis which I described before the Medico-Chirurgical Society in 1905. (See Plate 20.) The more serious congenital defects render the heart equally liable to infection, as seen in the following cases, which have all been treated at St. Bartholomew's during the past five years:—

*Case I.* A man, aged 31, admitted under the care of Dr. Samuel West. Previous illness, rheumatism at 24. Sudden onset of illness with dyspnoea and praecordial pain. Low intermittent fever, with albuminuria and haematuria. Heart enlarged; systolic apical and basal murmurs. Blood-culture yielded a growth of *streptococcus faecalis*. Duration of illness, fourteen weeks. *Post mortem*: the heart weighed 16 oz.; the tricuspid, mitral, and pulmonary valves were natural; the aortic valve was thickened and was the seat of fungating vegetations (Plate 19, Fig. 9). There was a hole in the membranous part of the interventricular septum, surrounded by a fibrous ring of endocardium and a few small vegetations. On the wall of the right ventricle, opposite to this hole, was a mass of fungating vegetations, spreading directly outwards from the perforation in the septum. These vegetations were implanted upon a patch of thickened endocardium. The infection had evidently been carried by the blood-stream from the aortic cusps, through the septum, to the wall of the right ventricle (Plate 19, Fig. 10). There were recent infarcts in the spleen and kidneys.

*Case II.* A woman, aged 42, admitted under the care of Dr. Ormerod. She had always suffered from shortness of breath, and had been told that she had congenital heart disease. No history of rheumatism or of other diseases. On admission pleural friction was heard in the left axilla, and later pericardial friction. The heart was enlarged; there were signs of mitral stenosis and regurgitation. Fever was present (98°—102°) of an irregular character. The heart rapidly failed and death took place a fortnight after admission. *Post mortem*: the heart weighed 18 oz.; the pericardium was inflamed; the mitral cusps were rolled up and thickened, with some fusion also. The aortic valve showed a large mass of warty vegetations on its cusps (Plate 19, Fig. 7). The tricuspid and pulmonary valves were natural and the foramen ovale was closed. A large mass of vegetations was present in the pulmonary artery, starting above at the lips of a patent ductus arteriosus and spreading downwards nearly as far as the pulmonary cusps. These vegetations occupied the part of the wall of the pulmonary artery lying away from the aorta (Plate 19, Fig. 8). The spleen weighed 19½ oz., and was large and soft. There were many haemorrhagic infarcts in the lung, and some pulmonary thrombosis in the right lower lobe. Cultures from the heart's blood and vegetations yielded pneumococci.

*Case III.* A boy, aged 7, was admitted under the care of Dr. Gee, in July, 1904, on account of short breath and cough. Bronchitis was present.

There was no cyanosis, but the fingers were somewhat clubbed. Quotidian intermittent fever, lasting for some three months, suggested infection of a congenitally defective heart, but two blood-cultures yielded no growth of micro-organisms. Eventually the fever subsided, though it did not completely disappear, and the boy was sent to a convalescent home. Three weeks later he returned to hospital, under the care of Dr. Herringham, again suffering from bronchitis. A very loud and prolonged systolic murmur was heard all over the chest and also at the back; its maximum intensity was over the pulmonary area and down the left border of the sternum. Six weeks later signs of kidney disease appeared,—haematuria, albuminuria, scanty urine, and oedema. There was practically no fever. The oedema increased and the boy eventually died, three months after his second admission and eight months after the onset of his illness. *Post mortem*: both right and left chambers of the heart were much dilated, as also were the mitral and tricuspid valves. Both ventricles were somewhat hypertrophied. The aortic, mitral, and tricuspid valve cusps were all natural. The pulmonary valve cusps showed numerous warty vegetations but no evidence of congenital disease. These vegetations spread a little way along the wall of the pulmonary artery. In the conus, just below the pulmonary valve, was a firm fibrous band, which had probably caused some pulmonary stenosis. The septum ventriculorum was patent above, by a hole as large as a sixpence. The heart's blood, the vegetations, and the spleen were sterile after cultivation, but the vegetations and heart-wall showed numerous masses of minute Gram-negative bacilli in section, probably influenza bacilli.

vii. *Valves, &c., affected by the disease.* In the 118 post-mortem examinations made on the series of 150 cases, the infection was found to be distributed as follows:—

| | |
|---|---|
| 1. Mitral cusps only | 38 |
| 2. Aortic cusps only | 22 |
| 3. Mitral and aortic cusps | 63 |
| 4. Tricuspid, with mitral or aortic or both | 14 |
| 5. Pulmonary cusps, with mitral or aortic or both | 7 |
| 6. Mural infection (auricular) | 43 |
| 7. Mural infection (ventricular) | 8 |

There was no instance of pulmonary or of tricuspid infection occurring alone. In infection of both of these valves the micro-organism present is in most cases the pneumococcus. Congenital defects were present in 8 cases. Mycotic aneurysms, ruptured or unruptured, were present in 20 cases—of the aortic cusps in 7, of the mitral cusps in 5, of the wall of the heart in 4, and of the interventricular septum in 4. (See Plate 18.)

Of the *characters of the vegetations* there is little to say. In the pneumococcal and gonococcal cases they are usually large single masses, sometimes pedunculated, friable, easily detached, often leaving little ulceration on removal. The chronic streptococcal cases are more apt to show extensive areas of ulceration, covered by small warty growths, showing haemorrhages and not seldom small sloughs. It is, however, often quite impossible to diagnose from the appearances of the vegetations in the post-mortem room the nature of the causal

microbe. Thus, in two of the influenzal cases which I have examined the growths were small and very localized (see Plate 20); but in a third case the vegetations were quite indistinguishable from those seen in many streptococcal cases. In Plate 19, Fig. 12, the large fibrinous masses of a pneumococcal case are well shown. Sections through the infected endocardium show infiltration of the tissues to a variable depth, chiefly depending upon the duration of the infection. Plate 18, Fig. 5 shows deep involvement of the connective-tissue layer of the mitral valve cusp by large masses of influenza bacilli.

viii. *Bacteriology.* Contrary to the experience of most observers in rheumatic fever, in which disease micro-organisms cannot be isolated from the blood or inflammatory exudates, carefully arranged blood-cultures in infective endocarditis usually yield a growth of some microbe of definite pathogenicity. The frequency with which blood-cultures are positive in this disease turns very largely upon the technique employed. When every facility is given to the micro-organism to grow in the media used it may be said that positive cultures are obtained sooner or later in the course of the disease in 90 per cent. of cases. In another place I have gone into details concerning the technique I usually employ, seeing that I regard the process as one of great importance in arriving at a correct diagnosis (*The Practitioner*, November, 1905). Summarizing the main points that are important, it may be said that—(*a*) a sufficient quantity of blood must be taken, not less than 5 c.c.; (*b*) to avoid contamination by air or skin the blood should be taken direct from a vein; (*c*) immediate transference of the blood to a series of broth-tubes should be made, mixing the blood and broth in different proportions in different tubes; (*d*) some at least of the tubes should be at once incubated at a temperature of 37·5° C.; (*e*) the absence of visible colonies of growth in 48 hours should not be taken as final: any tubes which appear sterile should now be well rolled and placed once more in the incubator, so that a minute but slowly growing colony may be encouraged to show itself. Plate 20, Figs. 17 and 18 show the results of two blood-cultures undertaken at an early and at a late stage in a subacute case of the disease. The isolation of the micro-organism from the blood-stream during life is so much more important in every way than its mere demonstration after death, almost excluding, as it does, the possibility of terminal infection, that I will deal first with results thus obtained.

*Blood-Cultures undertaken during life in* 32 *cases of Infective Endocarditis.*

This series includes those cases investigated during the years 1905–8. The technique adopted was that already referred to.

(i) *Positive Results.* (Twenty-nine cases.)

| No. | Sex | Age | Rheumatism or Other Illnesses | Duration of Illness before Culture | Duration after Culture | Micro-organism isolated |
|---|---|---|---|---|---|---|
| 1 | male | 13 | Two attacks rheumatic fever, last 2 years before this illness | 3 months | 2 months | Streptococcus |
| 2 | male | 12 | No previous illness | 10 days | 3 days | Streptococcus |
| 3 | male | 33 | Malaria some years previously | 7 weeks | 1 week | Streptococcus |
| 4 | female | 25 | Graves' disease immediately prior to illness | 3 months | 4 months | Streptococcus |
| 5 | male | 52 | Syphilis some years previously | 3 months | 2 months | Streptococcus |
| 6 | male | 44 | Rheumatic fever 19 years previously | 2 months | 1 month | Streptococcus |
| 7 | female | 17 | Rheumatic fever 8 years previously | 4 months | 2 months | Streptococcus |
| 8 | male | 52 | No illnesses | 4 months | Unknown | Streptococcus |
| 9 | male | 44 | Malaria, influenza | 5 weeks | 1 week | Streptococcus |
| 10 | male | 34 | No illnesses | ? 6 months | 2 weeks | Streptococcus |
| 11 | male | 28 | Rheumatic fever 10 years previously | 10 months | Unknown | Streptococcus |
| 12 | male | 30 | Rheumatic fever 5 years previously | 4 months | 6 weeks | Streptococcus |
| 13 | female | 31 | Rheumatic fever 14 years previously | 4 months | 7 weeks | Streptococcus |
| 14 | male | 39 | No illnesses | 9 months | 2 months | Streptococcus |
| 15 | male | 34 | Rheumatic fever 3 times, last 6 years previously | 6 weeks | Unknown | Streptococcus |
| 16 | female | 16 | Rheumatic fever 2 years previously | ? | 3 months | Streptococcus |
| 17 | male | 34 | 'Athlete's heart' 10 years duration | 2 months | 4 months | Streptococcus |
| 18 | male | 30 | No illnesses | 3 months | 2 months | Streptococcus |
| 19 | female | 24 | No illnesses | 3 months | 3 weeks | Streptococcus |
| 20 | male | 31 | Rheumatic fever 13 and 4 years previously | 10 weeks | 6 weeks | B. influenzae |
| 21 | male | 13 | No illnesses (? rheumatism) | 3 weeks | 5 weeks | B. influenzae |
| 22 | male | 44 | Rheumatic fever 27 years previously | 4 months | 2 weeks | B. influenzae |
| 23 | female | 35 | Rheumatic fever 10 years previously | 2 months | 2 months | B. influenzae |
| 24 | male | 37 | Syphilis some years previously | 2 months | 4 months | B. influenzae |
| 25 | male | 10 | Rheumatic fever followed by pneumonia and empyemata | 7 weeks | 2 weeks | Pneumococcus |
| 26 | male | 26 | No illnesses | 3 weeks | 10 days | Pneumococcus |
| 27 | male | 15 | No illnesses | 6 weeks | 2 weeks | Pneumococcus |
| 28 | male | 21 | Gonorrhoea | 4 weeks | 4 weeks | Gonococcus |
| 29 | female | 21 | No illnesses | 18 months | 2 weeks | Staphylococcus albus |

(ii) *Negative results.* (Three cases.)

| No. | Sex | Age | Rheumatism or Other Illnesses | Duration of Illness before Culture | Duration of Illness after Culture | Micro-organism isolated P.M. |
|---|---|---|---|---|---|---|
| 1 | male | 22 | No illnesses | ? 6 weeks | 2 weeks | Streptococcus |
| 2 | male | 37 | Rheumatic fever 20 years previously | 9 months | 1 month | Pneumococcus[1] |
| 3 | male | 39 | No illnesses | 2 months | 2 weeks | Gonococcus |

By the kindness of Dr. F. W. Andrewes I am able to add to the above 29 positive results 11 others obtained by himself and by his colleagues in the pathological department of St. Bartholomew's Hospital during the years 1907–8.

(iii) Eleven additional positive results of blood-culture undertaken during life in cases of infective endocarditis.

| No. | Sex | Age | Rheumatism or Other Illnesses | Duration of Illness before Culture | Duration after Culture | Micro-organism isolated |
|---|---|---|---|---|---|---|
| 30 | female | 25 | The disease followed operation for mastoiditis | 1 week | 1 week | Streptococcus |
| 31 | male | 52 | No illnesses | 3 months | 1 month | Streptococcus |
| 32 | female | 18 | Rheumatic fever 2 years previously | 6 weeks | ? | Streptococcus |
| 33 | male | 30 | Rheumatic fever 12 years previously | 4 months | 2 months | Streptococcus |
| 34 | female | 36 | Rheumatic fever 10 years previously | 3 months | 1 month | Streptococcus |
| 35 | female | 32 | The disease followed pyosalpinx | 2 months | 2 weeks | Streptococcus |
| 36 | female | 19 | Chorea 7 years previously and with onset of the disease | 3 months | 3 months | Streptococcus |
| 37 | female | 35 | Rheumatism 10 years previously | 3 months | 4 days | B. influenzae |
| 38 | female | 27 | Rheumatic fever 10 years previously | ? 2 months | 1 week | Pneumococcus |
| 39 | female | 23 | No illnesses | ? | 3 weeks | Gonococcus |
| 40 | male | 32 | No illnesses | 3 months | 1 month | Unclassified |

These 40 positive results of blood-culture constitute a series sufficiently large to justify an analysis of the micro-organisms obtained. In 27 of the cases post-mortem examinations were made, and in all of them the diagnosis was confirmed and the micro-organisms either cultivated or demonstrated in film preparations.

[1] This patient developed lobar pneumonia and pericarditis 4 days before death: the condition was probably a terminal infection by the pneumococcus. It is likely that the micro-organism causing the chronic infection of the endocardium was not isolated post mortem.

(iv) *Analysis of* 40 *positive results of blood-culture during life in Infective Endocarditis.*

| *Number of cases.* | *Micro-organism isolated.* |
|---|---|
| 26 | Streptococcus. |
| 5 | Bacillus influenzae. |
| 5 | Pneumococcus. |
| 2 | Gonococcus. |
| 1 | Staphylococcus albus. |
| 1 | Unclassified. |

From this analysis it follows that infective endocarditis is pre-eminently a form of streptococcal disease, for streptococci occur in 66 per cent. of all cases. If the pneumococcus be regarded as belonging to the genus streptococcus, which it undoubtedly does, the percentage of cases due to this microbe rises to over 77. The relatively high place taken in the series by Pfeiffer's bacillus may cause surprise, but this is in harmony with the view previously expressed by the writer with regard to the prevalence of this micro-organism in cases of infective endocarditis. Since the original description of two instances of influenzal endocarditis by the writer in 1905, and of a third in 1906, a fourth case has come before his notice (24 in the series). A fifth instance was discovered by Dr. Thursfield (37 in the series) in a patient admitted to St. Bartholomew's under the care of Dr. West. A sixth case was recently described very fully by Dr. Fred Smith. No other instances of successful cultivation of the influenza bacillus from the blood during life appear to have been recorded. The absence of staphylococcus aureus from this series is due to the fact that these cases are, with two exceptions, drawn from medical, and not from surgical sources. The commonest micro-organism causing endocarditis in surgical cases is undoubtedly staphylococcus aureus. It is not at all an uncommon terminal event in osteomyelitis. The cases are often of the fulminating type and there is little time for investigations by blood-culture. The micro-organism next in frequency in surgical cases appears to be streptococcus pyogenes. In both these instances, however, when a focus of pyogenic infection exists prior to the development of ulcerative endocarditis, the latter condition is an incident in the pyaemia rather than the source of it. This was so in the two cases in this series which were of surgical interest; they are nos. 30 and 35: in the former the fungating endocarditis was part of an acute streptococcal pyaemia following a radical operation for mastoid disease, in the latter it was secondary to pyosalpingitis.

The characters of the streptococci found in cases of infective endocarditis deserve special attention. Until recently no adequate means of differentiation of the streptococcus group of micro-organisms existed. But the researches of Dr. M. H. Gordon into certain metabolic reactions given by different strains of streptococci have provided a basis of classification which has been of great service. By means of these differential tests and certain other features shown

by the various strains examined, Dr. Andrewes and I were able to distinguish five main types of streptococci pathogenic for man having characters sufficiently distinct, despite the existence of many intermediate forms, to deserve type names (*Lancet*, Sept. 15, 22, and 29, 1906). These five types are as follows:—

| Types | Biochemical reactions | | | | | | | Growth on gelatin at 20° C. | Morphology in broth | Pathogenicity for mice |
|---|---|---|---|---|---|---|---|---|---|---|
| | Milk clotted | Acid in saccharose | Acid in lactose | Acid in raffinose | Acid in inulin | Acid in salicin | Acid in mannite | | | |
| 1. Streptococcus pyogenes | · | + | + | · | · | ± | · | + | longus | + |
| 2. Streptococcus salivarius | + | + | + | ± | · | · | · | ± | brevis | · |
| 3. Streptococcus anginosus | + | + | + | · | · | · | · | ± | longus | + |
| 4. Streptococcus faecalis | + | + | + | · | · | + | + | + | brevis | · |
| 5. Pneumococcus | ± | + | + | + | ± | · | · | · | brevis | + |

Applying this classification to the streptococci obtained in 31 cases of infective endocarditis by blood-culture, the result is as follows:—

1. Streptococcus pyogenes . . . . . 3 cases.
2. Streptococcus salivarius . . . . . 9 „
3. Streptococcus anginosus . . . . . 6 „
4. Streptococcus faecalis . . . . . 8 „
5. Pneumococcus . . . . . 5 „

This shows clearly that the type of streptococcus most often found in infective endocarditis is not the highly pathogenic streptococcus of suppurative processes (*S. pyogenes*; syn. *S. erysipelatis*), nor the equally virulent pneumococcus, but one or other of three types of streptococci that are more closely allied to the 'saprophytic' streptococci of the alimentary tract. Excluding the two surgical cases in the above series, both of which were due to streptococcus pyogenes, and the pneumococcus cases, which usually complicate pneumonia and run a rapid course, it may be said that infective endocarditis is due to the operation of streptococci of low virulence, of the types found in normal faeces and in normal saliva. They are for the most part short chained cocci, not pathogenic for mice, and yielding a set of biochemical reactions that mark them off quite sharply from streptococcus pyogenes. These facts harmonize with certain broad clinical and pathological principles connected with the disease and serve to explain them:—(i) The chronicity of many of the cases and the latency of the disease in others. (ii) The scanty or absent leucocytosis often seen in the disease. (iii) The afebrile periods which are common and the occasional absence of fever altogether. (iv) The absence of suppuration in the embolic infarcts which is such a feature of the disease, which is by some observers adduced as evidence that the associated endocarditis is of

rheumatic origin. (v) The absence of any visible focus of infection. (vi) The enormous number of living micro-organisms that may be present in the blood-stream without causing grave symptoms. It may be that the very lowness of the virulence of these habitual saprophytes of the alimentary canal accounts for the lack of efficient resistance on the part of the patient, there being no adequate stimulus to call forth the defensive mechanisms necessary for the destruction of the cocci. In connexion with the post-mortem observation so often made, that the infarcts in various organs in malignant endocarditis are rarely suppurative, it is interesting to refer to a case in which, during life, the blood-culture had yielded growth of streptococcus faecalis. At the autopsy it was found that the patient had general suppurative peritonitis secondary to the rupture of a suppurating splenic infarct. From the splenic abscess a growth of streptococcus pyogenes—long-chained and pathogenic for the mouse—was obtained; there had evidently taken place a late infection by this new strain of streptococcus, and this was indeed suggested by the change in the characters of the disease during the last few days of the patient's life.

It may here be remarked that it is possible to set up a condition of infective endocarditis in the rabbit by the intravenous injection of saprophytic streptococci from human saliva and faeces, as described by the writer in a report upon this subject published by the Local Government Board in the Medical Officer's Reports, 1906–1907.

The nature of the causal microbes in infective endocarditis has been dealt with in this series of positive blood-cultures, rather than in a series of post-mortem findings, because in this way terminal infections are almost, if not entirely excluded. It will be seen, for example, that in most of the cases the micro-organism was isolated some weeks, and occasionally some months, before death. A review of the bacteriology of the disease as ascertained in the post-mortem room yields, nevertheless, very similar results. The following is an analysis of the last 100 cases examined in this way at St. Bartholomew's Hospital, covering the years 1901–8 inclusive. The micro-organisms were isolated from the heart's blood, or vegetations, or both. In many cases they were also isolated from the spleen, and in some cases from the kidneys and other organs.

| *Micro-organism.* | *Number of cases.* |
|---|---|
| 1. Streptococcus | 62 |
| 2. Pneumococcus | 19 |
| 3. Staphylococcus aureus | 7 |
| 4. Pfeiffer's bacillus | 5 |
| 5. Gonococcus | 3 |
| 6. Streptococcus and staphylococcus | 1 |
| 7. B. Coli communis | 1 |
| 8. B. aerogenes capsulatus | 1 |
| 9. Unclassified | 1 |

The percentage of streptococcal cases obtained post mortem is therefore almost exactly the same as obtained ante mortem. Staphylococci are more fully represented post mortem than ante mortem on account of the fulminating nature of the disease when due to this micro-organism, oft-times giving little opportunity for clinical investigation. The additional two instances of influenzal infection were demonstrated by rubbings and sections of the vegetations, but not by actual culture, which appears to be rarely possible from tissues or blood after death. The single instance of colon bacillus infection was demonstrated by Dr. Andrewes, who has reported the fact elsewhere. It occurred in a boy aged 12 years, who had never suffered from rheumatism or scarlet fever. The duration of his illness was 4 months; there were present a systolic apical murmur, occasional rigors, and an enlarged spleen. Six weeks before death embolism occurred in the right brachial and femoral arteries. Post mortem there was found to be purulent peritonitis from rupture of a suppurating splenic infarct. The aortic cusps showed large lumpy vegetations, friable and easily detached; from them a pure culture of colon bacilli was obtained. On section these bacilli were demonstrated in enormous numbers in the valve tissues, arranged in long threads. The heart is pictured in Plate 18, Fig. 4.

The older accounts of the bacteriology of this disease were based wholly upon post-mortem findings, and it is highly probable that much of the heterogeneous flora sometimes described was the result of terminal infection, if not indeed of post-mortem invasion, of the heart's blood or surface of the endocardium. In some of these earlier accounts descriptions of micro-organisms appear which it is quite impossible now to recognize, on account of the developments which have taken place in methods of bacterial culture. This remark applies to much of the earlier work of Weichselbaum on this subject. An atypical form of streptococcus recently isolated by blood-culture on two occasions from one of the chronic cases (no. 36 in the series) by Dr. Hugh Thursfield, had many of the characters of the micro-organism called by Weichselbaum 'micrococcus endocarditis griseus'. This microbe was also isolated by Dr. Thursfield from the heart's blood, vegetations, spleen, and kidneys post mortem. The growth in the blood taken for the culture was very slow, colonies only appearing on the fourth day. The colonies on agar were very minute; they failed to appear either on agar or gelatin in the cool incubator. As regards morphology, the individual cocci were extremely small, and occurred in pairs, tetrads, and small groups of 10–20 members. Gram staining was positive. Lactose was the only sugar fermented; milk was not clotted. The cocci obtained post mortem also fermented saccharose. Pathogenicity was slow in mice, killing by septicaemia in 9–10 days. Micro-organisms difficult to classify are not seldom obtained from cases of infective endocarditis, even during life. In addition to the above-mentioned instance, another occurred amongst the series analysed on p. 296, i. e. no. 40. This was obtained on three separate occasions in blood-cultures by Dr. Harold Pritchard. It was a short, slender bacillus, non-motile, doubtful in its reaction

to Gram's stain, showing uniform staining with ordinary dyes, growing well at 37° C. on all ordinary media, but not at all at the room temperature, and only very feebly on gelatin at 22° C., without liquefaction. The colonies on agar were small, round and discrete, resembling colonies of the pneumococcus. No sugars were fermented. Cultures died out readily if not transplanted in 3–4 days. Pathogenicity: mice were killed in twenty-four hours, and a rabbit, which had received an intravenous injection of the bacilli, died septicaemic on the sixth day. The same microbe was isolated from the patient's blood and vegetations post mortem.

ix. *Age-incidence.* Of the 150 cases analysed the age-incidence is as follows:—

| | |
|---|---|
| Under 5 years old | 2 cases. |
| From 5 to 10 years | 5 „ |
| „ 10 to 15 „ | 9 „ |
| „ 15 to 20 „ | 29 „ |
| „ 20 to 30 „ | 39 „ |
| „ 30 to 40 „ | 31 „ |
| „ 40 to 50 „ | 23 „ |
| „ 50 to 60 „ | 8 „ |
| Over 60 „ | 4 „ |

The chief incidence of the disease is thus seen to come between the ages of 15 and 50; half of all the cases occur between the ages of 20 and 40, no doubt on account of the predisposition created by the presence of sclerosis of the heart-valves after acute rheumatism, the chief age-incidence of which is a decade earlier than this. The youngest case in the series was that of a child aged $2\frac{1}{2}$ years, in whom the disease complicated congenital heart defects. The oldest cases were those of a man aged 63 and a woman aged 64 who both developed pneumococcal endocarditis with lobar pneumonia.

x. *Sex.* The sexes are almost equally divided: 79 cases occurred in males, 71 in females, out of the series of 150.

xi. *Forms of the disease.* There are three main forms of the disease: *acute*, *sub-acute*, and *chronic*. There are also two secondary forms: *acute fulminating* and *chronic latent*. The secondary forms are not of great clinical interest. They scarcely admit of specific treatment, and they are invariably fatal. The latent form, from its nature, is only discovered post mortem. The fulminating form may sometimes be suspected but is rarely diagnosed.

(i) *Latent infective Endocarditis.* Usually a terminal condition in old-standing cases of valvular disease. Less often a terminal condition in nephritis or in cirrhosis of the liver. The patient has usually been treated for these primary conditions for some time, but not seldom comes under observation in hospital practice a few days up to a week or two before the fatal issue. In

either case he is seen to be very ill, suffering from an exacerbation of his wonted state of cardiac, renal, or hepatic disorder. There may be slight fever, or the condition may be afebrile. In many of the cases there appears to be a gradual failure of the functions of all three of the organs above mentioned, a state of such lowered vitality that it is small wonder that micro-organisms from the alimentary canal have little difficulty in finding a nidus upon the ill-nourished and sclerosed mitral cusps. Haemorrhagic tendencies are common at the close of all these chronic diseases, so that haematuria and petechiae, though in the light of the post-mortem findings they are probably to be referred to the state of the endocardium, may not direct the physician's attention to the possibility of valvular infection during life. Under this heading may also be put the cases in which a sudden fatal event occurs in a person who is not known to be suffering from any illness. Such are the cases brought comatose to the hospital, and dying of cerebral haemorrhage. The micro-organism present is almost always a faecal or a salivary streptococcus.

(ii) *Fulminating infective Endocarditis.* The following instance of this form of the disease suffices to characterize its main features: A woman, aged 53, suffered from periostitis and necrosis of the fifth rib, close to the sternum, after typhoid fever. The rib was scraped and a small sinus resulted. Three years later this small sinus was still present. The woman attended at the hospital and it was again scraped, under nitrous oxide, without admission to the wards. Whilst attending in the casualty department, two days later, in order to have the part dressed, the patient had a rigor; the temperature was found to be 105·5°, and she was admitted under the care of Sir Dyce Duckworth. She was drowsy, and complained of no pain or discomfort. The heart was dilated but no murmurs were heard. Examination of the rib-sinus revealed nothing amiss. The spleen was not felt. The urine was natural. On the second day the patient's colour became dusky; she continued to be drowsy; the fever remained high; the rigor was repeated. On the third day she died, comatose and cyanosed, with a temperature of 107·5°. (See Chart 1.) At the post-mortem examination recent fungating vegetations were found on the mitral and aortic valve cusps, and a small mycotic aneurysm had formed upon the base of the anterior mitral flap. The micro-organism isolated from the vegetations and from a small collection of pus lying at the end of the rib-sinus was staphylococcus aureus. Most of these fulminating cases are due to this micro-organism, and in most of them there is a definite focus of infection, as in this case. Osteomyelitis is the focus in not a few. Streptococcus pyogenes occasionally causes a very rapidly fatal form of the disease, and the pneumococcus also. In the pneumococcal cases there is usually present consolidation of the lung also, and not infrequently a pneumococcal suppurating meningitis in addition.

(iii) *Acute infective Endocarditis.* The onset is usually abrupt, often with a rigor (13 out of 27 cases), and the symptoms are those of an acute specific fever. Pain in, and swelling of, joints are common (5 cases), oft-times leading to a diagnosis of rheumatic fever and justifying the exhibition of salicylates.

The pneumococcal group comes almost wholly under this head, and the onset here is usually that of pneumonia (10 cases) or of pleurisy with effusion (3 cases). No crisis comes with the eighth day of the disease, but the patient remains acutely ill. Besides the pneumococcus the micro-organisms most commonly met with are streptococcus pyogenes and staphylococcus aureus. The gonococcus cases also appear to be of this form. The duration of the cases is between seven and thirty days. Undoubtedly a very few cases recover.

(iv) *Subacute infective Endocarditis.* The commonest form (88 cases in 150). The *onset* is usually rather insidious, and takes one or other of the following lines:—(*a*) Shortness of breath with or without praecordial pain and discomfort, or oedema (32 cases). This evidently represents the cardiac group of

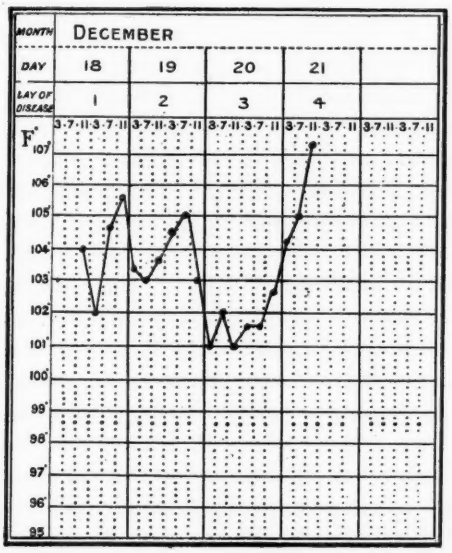



CHART 1. Illustrating a form of fever in the fulminating type of acute infective endocarditis. Death on fourth day of disease.

some authors, and means that the changes taking place at the valves, and the consequent state of septicaemia, are causing dilatation of the hitherto compensated and quiescent heart-muscle. (*b*) General weakness (18 cases), often with loss of flesh, or pains in the limbs or abdomen, or cough, or painful joints. (*c*) A condition simulating subacute rheumatism, and sometimes indistinguishable from it (6 cases); occasionally chorea (3 cases). (*d*) Fever unexplained by other physical signs (6 cases). This form of onset is chiefly seen amongst private patients, who come under observation earlier than hospital patients and are discovered to have a raised temperature with little else except slight malaise.

The duration of these subacute cases, which form the largest group, is from two to six months. The micro-organisms chiefly causing them are the faecal and

salivary types of streptococci, the influenza bacillus, and, less often, the pneumococcus.

(v) *Chronic infective Endocarditis.* A less common form of the disease, yet of quite frequent occurrence. 18 of the 150 cases have been of this kind. The onset is most insidious; so insidious, indeed, that it is often impossible to say when the disease began. And this is equally so whether the patient be of the hospital class and comes under observation late in the course of the disease, or of the private class, and keeps fairly well in touch with his doctor. In many instances an extraordinary sanguineness of temper, which is a striking feature in the patients, prevents them from drawing the attention of their medical man to what they persist in regarding as quite trivial symptoms. Dr. Norman Moore referred to this feature at the meeting of the Association of Physicians and considered it to be of help in diagnosis. In one of these chronic cases, himself a doctor, it was quite impossible to get the patient to take a serious view of his illness, and he absolutely refused to lie up or be treated, but continued to assist in his practice long after his blood had been demonstrated to contain large numbers of micro-organisms. As already remarked, the pre-existing heart lesion in some of these cases is very slight, although its presence is usually known if the patient is of the private class. A very slowly progressing loss of flesh, slight anaemia, some irregular fever and occasional sweating, vague pains in the limbs or joints or fingers or toes, areas of redness and tenderness on the hands or feet, one or more of these form the initial symptoms in the case. Examination reveals the signs of mitral or aortic disease, perhaps some hypertrophy, but little or no dilatation of the heart. Search may discover a palpable spleen, or a few red blood-cells in the urine, or a few small petechiae on the skin; but these more incriminating points may still be in abeyance. A blood-culture may, and usually does, even at this early stage, yield a positive result. The micro-organism is nearly always a streptococcus of the faecal or salivary sort; much less often Pfeiffer's bacillus; rarely a white staphylococcus. The duration of the disease is from six to eighteen months, sometimes longer. The single staphylococcal case which I have seen lasted certainly two years, possibly two years and a half. In this case the terminal event was uraemia. An autopsy was obtained, and the only area of infection was a small patch on the wall of the left auricle, the valve cusps being quite free. (See Plate 18, Fig. 6.) These chronic cases usually go quite unsuspected for a considerable part of their course. If the patients seek advice for one or other of their symptoms, the absence of anything suggesting acute illness is apt to throw the medical adviser off his guard. If they are treated in the out-patient department at hospitals, their condition is considered one of chronic valvular disease simply, and they may even be admitted as in-patients and discharged without the infection of their endocardium being revealed. This is largely because the degree of fever may be so slight and so irregular as not to attract attention. The first event to direct attention to the real state of affairs may be embolism, or even this may go unnoticed and a later effect of the embolism be discovered. Thus a hemiplegia may be the first warning, or, as in

a case already mentioned, the patient may first of all complain of an aneurysmal swelling at some part of his body.

xii. *Signs.* The signs of infective endocarditis are three: (*a*) the presence of valvular disease, as determined by examination of the heart, (*b*) the occurrence of embolism, and (*c*) the discovery of micro-organisms in the blood-stream. If these three signs concur in any case the diagnosis of infective endocarditis may confidently be made; the concurrence of any two of these signs makes the existence of the disease highly probable.

(i) *The presence of valvular disease.* In the great majority of cases signs of valvular disease are present at the very onset of the disease; in practically all the cases these signs are present sooner or later in the course of the disease. The cases fall into four groups as regards this question of valvular disease.

(*a*) Evidence of well-marked valvular disease is present before the commencement of the illness. This evidence may point to acquired or to congenital disease of the heart. This group is undoubtedly the largest, although it is not possible to prove this statement by figures; for the point cannot be settled by analysis of hospital patients, who usually come for treatment after the disease is well developed. Of twelve cases of the disease seen in private practice 'heart disease' was known to have been present by the patients' doctors in no less than nine. The great preponderance of 'secondary' over 'primary' cases of the disease is also borne out by the prevalence of signs of old-standing valve lesions in post-mortem observations. Thus out of 118 post-mortem examinations made in the series of 150 cases, no less than 94, or 80 per cent., showed signs of old valve lesions. In only 10 cases, or 8·4 per cent., was the infection found to be primary on previously healthy valves. In 14 cases, or 11·8 per cent., the point was doubtful. (The existence of old valvular disease was determined by the degree of hypertrophy of the heart-wall, and by the presence and amount of sclerosis of the valve cusps and of the mural endocardium.) The nature of the heart lesion, and its cause, are very variable. In most cases the lesion is mitral and the cause is acute rheumatism, from which the patient has previously suffered. The lesion may be attributed to athletics or to other forms of strain. Quite often no adequate cause can be assigned for the known valvular defect, which, though often slight and well compensated, is still easily manifest on examination. It is often a striking feature in the chronic cases of the disease that the valvular defect is of this slight degree and of doubtful origin, and these facts not seldom mislead the physician into disregarding the importance of the murmur which he hears over the heart. But in truth it may be said that any valvular lesion, however well compensated and whatever its duration or origin, will suffice as the basis of streptococcal infection.

(*b*) Evidence of valvular disease appears with the onset and early development of the disease. A much smaller group of cases, constituting the instances of primary infection, less than 10 per cent. in number. It must be remembered

that the evidence of previous valvular disease, if only slight, may easily be overlooked if attention be not specially given to the heart from the first; the primary cases are, perhaps on this account, not really so common as is generally thought, if the evidence of the post-mortem room be believed. These primary cases are usually due to the more acute infective microbes—streptococcus pyogenes, pneumococcus, staphylococcus aureus, and the gonococcus. Fig. 11, Plate 19, shows a primary gonococcus infection of the aortic valve. The unaffected cusp is seen to be thin and flexible. The heart was only slightly hypertrophied.

(*c*) Evidence of valvular disease appears late in the course of the infective endocarditis. This is unusual, but is quite well known to occur. It was so in Case III on p. 292; in this boy no heart-murmur was heard during the first six months of his illness, whilst he was under the care of Dr. Gee. He left hospital for a convalescent home, his condition having improved, though the fever was still present. On his return to hospital after three weeks, under Dr. Herringham, a loud murmur was heard at the pulmonary base and down the left border of the sternum. He lived three months after this murmur was first heard. Post mortem, an infection of the pulmonary valves by influenza bacilli was revealed.

(*d*) There may be no evidence of valvular disease at any time. This is rare, and is almost confined to cases in which the infection is of a terminal kind and occurring in patients who are too ill to admit of thorough examination. It is not very unusual to find in the post-mortem room, in patients dying of pneumonia, and who showed no signs of valvular disease, masses of vegetations attached to the heart valves.

The course taken by the signs of the heart lesion is variable. Undue importance is perhaps attached to changes heard in the character of the murmurs from day to day. These changes do certainly occur, but they are not of great importance. They are prone to occur in acute or in chronic endocarditis without infection. As the disease progresses it is common to get evidence of the involvement of other valves than that originally diseased, or of other defects in the same valve. One of the commonest developments is the appearance of the signs of aortic regurgitation in a case originally of mitral disease; another is the gradual appearance of the signs of mitral obstruction where at first was only mitral incompetence. The significance of these changes in regard to diagnosis is obvious. In Plate 18, Figs. 3 and 5 show an extreme degree of obstruction at the mitral orifice; in Fig. 3 the block is due to one large thrombotic mass, in Fig. 5 it is due to a number of warty growths.

The ultimate condition of the heart turns upon the nature of the terminal event. About 44 per cent. of the cases (66 in my series of 150) died with signs of heart failure.

(ii) *The occurrence of embolism.* The plugging of arteries, arterioles, and capillaries by pieces of vegetation detached from the endocardium constitutes one of the cardinal signs of the disease. This occurrence is extremely common; it is indeed doubtful if any case runs its whole course without embolism taking

place somewhere. In a few cases this occurrence may only be made apparent on post-mortem examination, but in the great majority of cases a careful search will reveal the signs of embolism during life. The importance of this search cannot be overestimated, as the diagnosis of the disease turns largely upon the discovery of the emboli. Sometimes the occurrence of embolism constitutes the first symptom. The effects of embolism are four: infarction, aneurysm, hæmorrhage, and inflammation with or without suppuration. The following are the situations in which embolism and its effects occur :—

(*a*) *The spleen.* Infarction of this organ is very common and enlargement of the spleen constitutes an important sign of the disease. This was noted in 47 of the series of 150 cases. If the chronic cases only were considered, a palpable spleen would certainly be found in a larger percentage of cases than these figures give. Splenic infarct often gives rise to acute pain, referred to the left hypochondrium or to the epigastrium, with abdominal tenderness. Friction may be heard over the enlarged organ, from the presence of perisplenitis. These acute abdominal symptoms not infrequently usher in the disease so far as symptoms are concerned. In the chronic cases the spleen, if palpable, usually feels firm; in more acute cases it is apt to be soft, presenting an ill-defined fullness in the left hypochondrium rather than a distinct tumour. Occasionally the spleen may be quite large, yet not palpable; at the post-mortem examination this is sometimes found to be due to the presence of an unusually well-developed costo-splenic ligament, forming a shelf on which the organ rests. The perisplenitis may give rise to pleurisy on the left side, even pleurisy with effusion. In a case of influenzal endocarditis, seen with Dr. Harold Scolefield, this pleurisy was the first sign of anything amiss with the patient. The effusion was aspirated, and the patient's health improved, but the fever, which was discovered at the time of the pleurisy, did not pass off, and a blood-culture revealed the true nature of the disease. Suppuration of the splenic infarct occurs only in the acute cases, when the infective agent is streptococcus pyogenes or staphylococcus aureus; it does not occur in the chronic cases.

(*b*) *The kidney.* Embolism causing renal infarction is as common as a similar condition in the spleen. The sign is haematuria. This sign is only recorded 46 times in the 150 cases, but this almost certainly refers to the gross haemorrhages which are manifest to the naked eye in examining the urine. In many cases the haemorrhage is too trivial to be thus discovered, or even by the aid of the guaiacum test: the microscope is needed for its detection. Until the urine has been repeatedly examined in this way with negative results it cannot be said that renal infarction is not taking place. Dr. Hale White commented upon this fact at the meeting of the Association of Physicians during the discussion on Prof. Osler's paper. The haematuria is often followed by albuminuria; intermittent albuminuria should always suggest renal infarction. A study of the kidneys found post mortem in infective endocarditis often suggests that a more frequent and more minute clinical examination of the urine than is often carried out would frequently demonstrate the existence of

emboli in these organs. Innumerable small haemorrhages are seen beneath the capsule; as these haemorrhages are situated on the pale background of an anaemic and often fatty kidney, their appearance is often very striking. Plate 17 illustrates very well the kidneys from a case of influenzal endocarditis. I believe this kind of kidney is spoken of in the dead house at Guy's as the 'flea-bitten' kidney. I have on two or three occasions cut sections of such a kidney; the microscopic examination shows very little, the appearances being chiefly due to colour changes. One characteristic appearance under the microscope, however, is a number of small areas of round-celled infiltration immediately beneath the capsule, as though consequent upon the irritation of small haemorrhages or minute infarcts in this region. Dr. Thursfield has several times shown me sections of kidneys from cases of infective endocarditis with a similar appearance.

(*c*) *The skin.* A very striking and fairly common manifestation of the disease is the occurrence of *petechiae* in the skin. These petechiae are generally attributed to small haemorrhages following minute emboli lodged in the arterioles of the skin. I have failed, in two cases, to demonstrate such emboli microscopically, the only change seen being the actual haemorrhage. Be this as it may, the existence of these skin haemorrhages should always be borne in mind and a careful search be made for them. They usually appear in crops, each group of petechiae lasting from one to several days. They are sometimes exceedingly numerous, so much so that the whole body may be covered with punctate spots and ecchymotic blotches. This was so in a patient sent up from Farnham by Dr. Hussey, and admitted to St. Bartholomew's under the care of Sir Dyce Duckworth. In this man, who was suffering from a streptococcal infection of the aortic cusps, the purpura was a very early sign. These haemorrhages into the skin were noted as present in no fewer than 43 of the 150 cases in my series. In 10 cases they appeared on the legs only, in 18 on the legs and elsewhere. Other common situations are the chest, neck, backs of wrists and hands, shoulders, and buttocks. In one case the only part in which the haemorrhage occurred was the lobe of one ear. In 4 cases they are noted as being present all over the body. In my experience a favourite site for their early appearance is the neck and upper part of the chest. Their significance in a doubtful case of the disease cannot be overestimated.

It is probable that the *tender spots* which are such a definite feature in some of the chronic cases, and to the significance of which Prof. Osler alluded in his recent paper, are also of embolic origin. They are not infrequently accompanied by a dusky discoloration of the skin at the affected part. Like the petechiae they may come and go. The pads of the thumbs, fingers, and toes are liable to these areas of discoloration and tenderness, and I have seen them on the heels and over the instep. In some cases the whole of a terminal phalanx may become tender to touch and very painful, and I have elsewhere alluded to the importance of recognizing the meaning of such localized conditions in patients with old-standing valvular lesions.

(*d*) *The brain.* Cerebral embolism, causing various paralytic and irritative nervous disturbances, is common. Evidence of the plugging of cerebral arteries was present in 22 of the 150 cases. It took the form of *hemiplegia* in 17 cases, right hemiplegia in 9, left hemiplegia in 8. In one case, of influenzal endocarditis, right hemiplegia was followed after an interval of three weeks by left hemiplegia; the patient became comatose and died three days later. Hemiplegia may be the first symptom of the disease, until then latent (3 cases). *Monoplegia* occurred in 3 cases,—of facial type in 2, of brachial in 1. *Cerebral haemorrhage* may follow embolism, by a sequence first demonstrated by Sir Richard Douglas Powell. Or haemorrhage may occur without any previous warning of a paralytic or other nature. Like embolism, the haemorrhage may be the first event of a serious nature in a latent case of the disease. It may cause sudden death in this disease. A patient was brought to the hospital by the police in a state of coma, and died in twenty-four hours. Post mortem: there were found two large subarachnoid haemorrhages over the frontal lobes, and a small haemorrhage into the substance of the pons. The aortic and mitral cusps and the wall of the left auricle contained large masses of vegetations. Multiple haemorrhages into the meninges (10 cases in 118 post mortems) are commoner than haemorrhage into the brain substance (4 cases). Though difficult to prove, these meningeal haemorrhages are probably due to small emboli.

The occurrence of *choreiform movements* is of special interest. They ushered in the disease in 4 of the cases, and they developed during the course of the disease in 3 cases. In one of the latter instances there was facial palsy of the supranuclear type, nystagmus, and partial ophthalmoplegia also. It would obviously be fallacious to conclude that any micro-organism isolated from the blood of a patient with fever, endocarditis, and chorea had any necessary connexion with the cause of rheumatic fever. The presence of these movements in infective endocarditis is suggestive in the light of Kirkes' theory of the cause of chorea.

(*e*) *The retinae.* Retinal haemorrhages are noted in 5 of the 150 cases, a figure which probably gives too low an estimate of the frequency of this condition. Like small haemorrhages into the kidneys causing transient and slight haematuria, and like occasional petechiae in the skin, small retinal haemorrhages may often be overlooked if not searched for. Amblyopia or a central scotoma due to retinal haemorrhage may occasionally be an initial symptom of the disease. No case of embolism of the central artery appears among these 150 cases.

(*f*) *The limbs.* Embolism of the large vessels of the arm or leg is not very common (6 cases: brachial 2, popliteal 2, femoral 1, ulnar 1). One of the influenzal cases developed, quite early, an infective *aneurysm* at the origin of the posterior tibial on the right side, causing great pain, which was at first mistaken for sciatica. The sac of the aneurysm grew to a large size and bulged into the popliteal space. Prior to this, however, some petechiae on the skin, and the presence of an aortic regurgitant murmur, had led to a blood-culture

and the isolation of Pfeiffer's bacillus in small numbers. Under treatment by vaccine the sac of the aneurysm slowly underwent retrogressive changes, and finally became completely thrombosed. Three months later, however, the patient died. A post-mortem examination showed the sac to be a false one; the posterior wall was formed of the periosteum of the upper part of the tibia, to which the blood-clot was firmly adherent. The following case of multiple aneurysms due to infective endocarditis shows how latent the disease may be:—

A man, aged 58, was admitted to the Great Northern Hospital, under the care of Mr. Mower White, on account of a small aneurysm seated on the right ulnar artery at its commencement. The aneurysm had appeared as a very tender painful swelling one month previously; it had since become smaller, but was still very painful. Abdominal examination revealed nothing, but *per rectum* two small, hard, round lumps were felt through the mucous membrane of the bowel as high as the finger could reach; these were thought to be enlarged glands. The aneurysm was removed on March 30. On April 12 the patient was noticed to be getting weaker, and the tongue was dry; the mental condition was apathetic; there was loss of flesh. On April 14 the first sound of the heart was found to be abnormal at the apex and at the base. On April 17 the patient became gradually unconscious, and he died two days later. There had been slight irregular fever since the operation. At the post-mortem examination there was found to be old and recent endocarditis of the aortic and mitral valves, the recent vegetations being of the verrucose kind. There was a large double sacculated aneurysm of the superior mesenteric artery (the tumour which had been felt *per rectum* during life), and another, smaller aneurysm on the hepatic artery. There was a recent haemorrhage into the left lobe of the cerebellum. There were recent and old infarcts in the spleen and in the liver.

(*g*) *The heart.* Plugging of a coronary artery may occur, and may lead either to sudden death or to infarction of the heart-wall; the infarct may lead to an aneurysm, which may rupture, and this, again, may cause sudden death. Diagnosis of these events is not possible, for the causes of sudden death in infective endocarditis are several (see p. 317).

(*h*) *Other Emboli.* In one case of this series an external carotid artery became plugged, the common iliac artery in another, the gastric in a third, and the superior mesenteric artery in a fourth. In the case of gastric embolism an attack of sudden abdominal pain marked the lodgement of the embolus. Abdominal pain, showing itself in recurrent attacks, is quite common in the disease. In some cases the cause is undoubtedly splenic infarction and perisplenitis; in some others it is probably associated with small mesenteric and omental haemorrhages, which are so frequently found when examination is made in the dead house.

(iii) *The presence of micro-organisms in the blood-stream.* The association of a valvular lesion with multiple embolism suggests infective endocarditis; the discovery of micro-organisms in the blood confirms it. I have already said that I consider the demonstration of these micro-organisms to be possible in about 90 per cent. of the cases, provided sufficient care be taken to encourage the growth of any bacterium present in the circulation. It is a striking feature

of the disease that living micro-organisms may exist in the blood, often to the extent of many thousands, without the patient showing any signs of being acutely ill. In one of the influenzal cases which I described, I estimated that the blood-culture yielded some 20–24 micro-organisms to the cubic centimetre; in one of the streptococcal cases the yield was even greater than this, probably as high as 30–40. In neither of the cases was there the outward appearance of acute illness. Reckoning the total amount of blood present in the body of an adult as five litres, this would mean that some 120,000 and 200,000 micro-organisms, respectively, were circulating in the bodies of these two patients.

It is probable that the septicaemic stage of the disease, during which micro-organisms exist in the blood-stream and probably multiply there, is preceded by a stage during which the blood is sterile, or nearly so. For it is certain that several negative blood-cultures may sometimes be followed by one or more positive cultures after an interval of time. Unfortunately for the needs of treatment, the isolation of the microbe is essential if anything of a specific nature is aimed at in an effort to combat its effects. Otherwise there is no doubt that treatment should be commenced before the septicaemic stage, whilst the infection is still localized to the endocardium.

xiii. *Symptoms.* The initial symptoms at the onset of the disease have been already dealt with (p. 303). Those seen during its course may be considered under the following heads:—

(i) *Fever.* Some degree of fever is present in most cases, though not in all. When it is absent (5 cases in 150), the disease is usually quite latent and unsuspected; moreover, the patient is then apt to be suffering from that general lowering of vitality referred to in the paragraph dealing with the latent form of the disease. It is unlikely that these (*a*) *afebrile cases* are afebrile throughout the whole course of the disease; it is most probable that they happen to come under observation at a time when the febrile phase of their illness has ceased. A patient, under the care of Dr. Morley Fletcher, was in St. Bartholomew's Hospital for fourteen days before he died, and there was no rise of temperature during the whole of this time. At the post-mortem examination the aortic and mitral cusps showed old and recent endocarditis, there was a mycotic aneurysm of the wall of the left ventricle, and there were recent infarcts in spleen and kidneys. The causal microbe was a short streptococcus.

The types of fever seen in the cases vary considerably. In the acute cases (*b*) a fairly high *continued fever* is common; it occurred in 12 cases. (See Chart 2.) It is seen in several of the pneumococcal cases when pneumonia is also present. This type is not seen in the chronic cases, but not seldom it occurs at the beginning of the subacute form of the disease, and lasts for a week or two, when it changes to an intermitting form, possibly concurrent with ulcerating changes in the heart-valves and the dissemination of infective emboli (10 cases).

(*c*) *An irregular remittent fever* is the commonest type in the chronic cases, and may occur in the subacute cases also (37 cases). Like the continued

form of fever it may pass into a series of larger oscillations, and fairly regular intermissions at a later stage of the disease, probably again concurring with ulceration and a more regular state of septicaemia (Chart 3). This irregular remittent type may be quite mild as regards the actual extent of the fever, as seen in Chart 4, which represents three weeks' temperatures from a case of chronic streptococcal endocarditis. *Afebrile periods*, lasting from two to six days or a little longer, are common in the course of such a type of fever, especially in the chronic cases. (See Chart 5.)

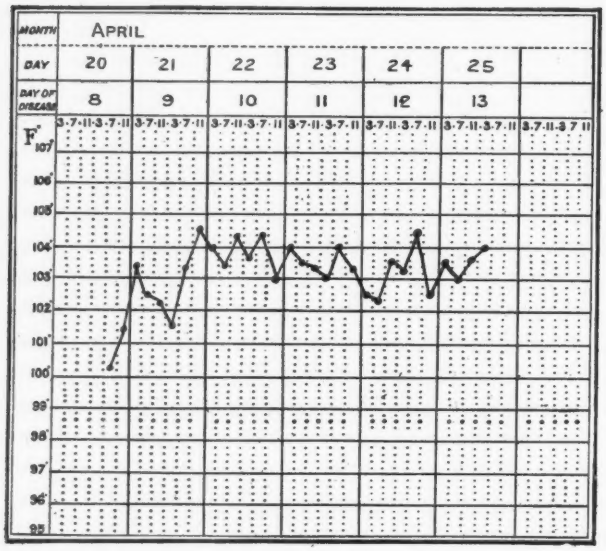



CHART 2. Illustrating the continued fever seen in many cases of acute infective endocarditis. Death on thirteenth day of disease.

(*d*) A high and *regular quotidian intermittent fever* is seen in some of the acute cases throughout, and in the later stages of the subacute cases sometimes (40 cases). The gonococcal cases appear to run this type of fever quite constantly. Chart 6 represents a fortnight of such fever in a case of gonococcal endocarditis under the care of Dr. Ormerod in 1904. It will be noticed that there are often two large intermissions of the temperature on each day. Chart 7 shows a very close similarity in these respects; it is from a case of gonococcal endocarditis recently under the care of Dr. Herringham. A similar state of things was well shown in a chart of a gonococcal case recorded by Harris and

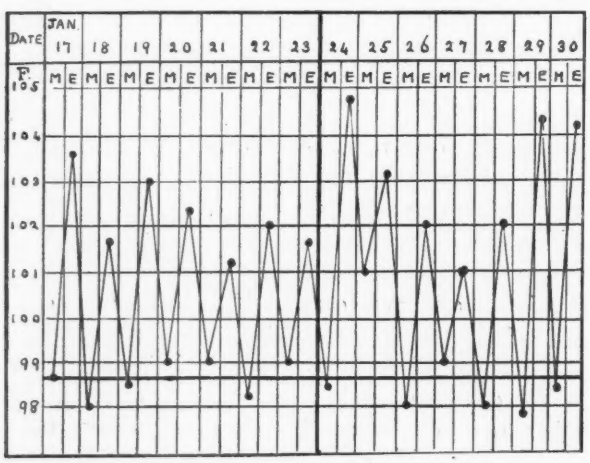



CHART 3. Showing large oscillations present in the late stage of a subacute case.

Johnston in the *Johns Hopkins Bulletin* for October, 1902. In any of the cases showing intermittent fever *sweats* are liable to occur, and in some instances the periodicity of these suggests the presence of malaria, as in a patient with gonococcal endocarditis recently under the care of Dr. Tooth. *Rigors* are not

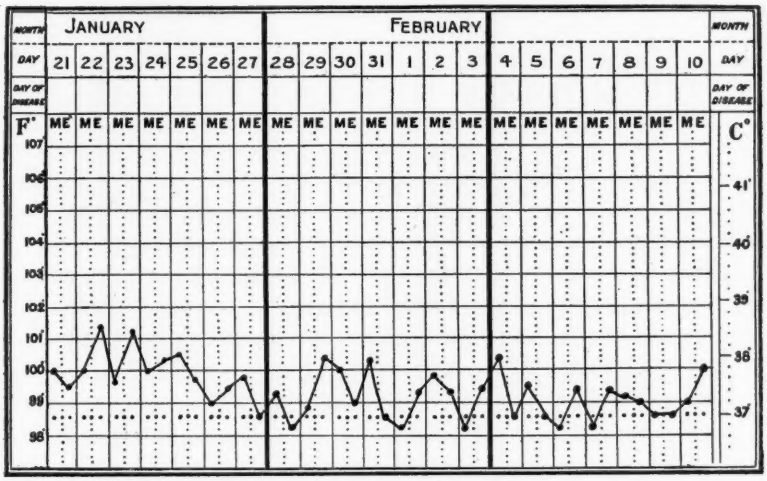



CHART 4. Showing the mild degree of fever which is often present in chronic cases.

very common in the disease, and are almost confined to the fulminating and acute cases. They were present in 25 cases only.

Whatever the form of fever in this disease the temperature is apt to take a lower range, or even to cease altogether, shortly before death. A fall in the

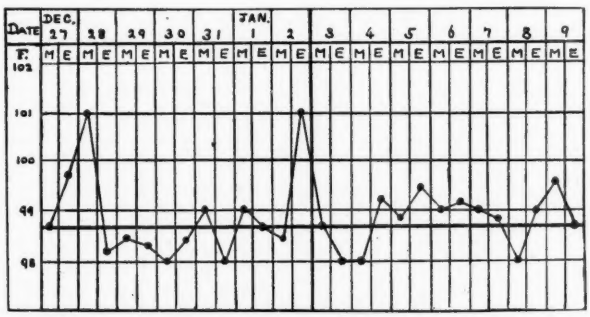



CHART 5. Showing afebrile periods present in chronic cases.

temperature, the patient remaining very ill, is of no service, and must not be mistaken for a good prognostic. I have noticed that this fall of temperature is very prone to occur when signs of renal inadequacy supervene. It was so in the very high intermitting fever of Dr. Ormerod's gonococcal case (Charts 8 and 9); it was also strikingly illustrated in the case of congenital heart disease referred to as Case III on p. 292. Whilst under Dr. Gee's care the patient's temperature was very high at times, and was still present on leaving hospital for the con-

valescent home. When readmitted to hospital under Dr. Herringham signs of nephritis developed, and for nearly two months before death the temperature was

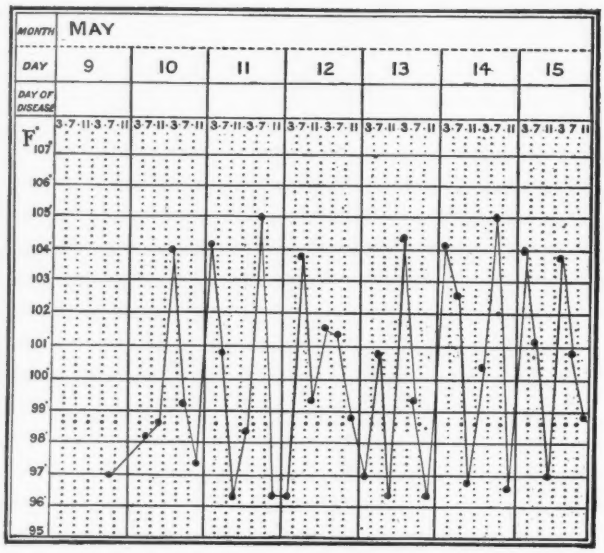



CHART 6. Showing wide oscillations, with double quotidian intermissions, in gonococcal endocarditis.

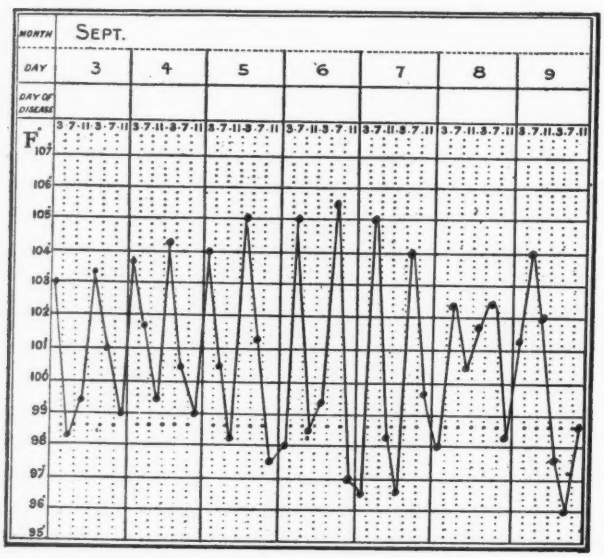



CHART 7. Showing double quotidian intermittent fever common in gonococcal endocarditis.

practically normal. The point is illustrated in several other cases in this series.

(ii) *Anaemia.* Progressive anaemia is usually a marked feature. In some

of the cases it becomes extreme, even suggesting the blood picture of pernicious anaemia. This is independent of the nature of the micro-organism present:

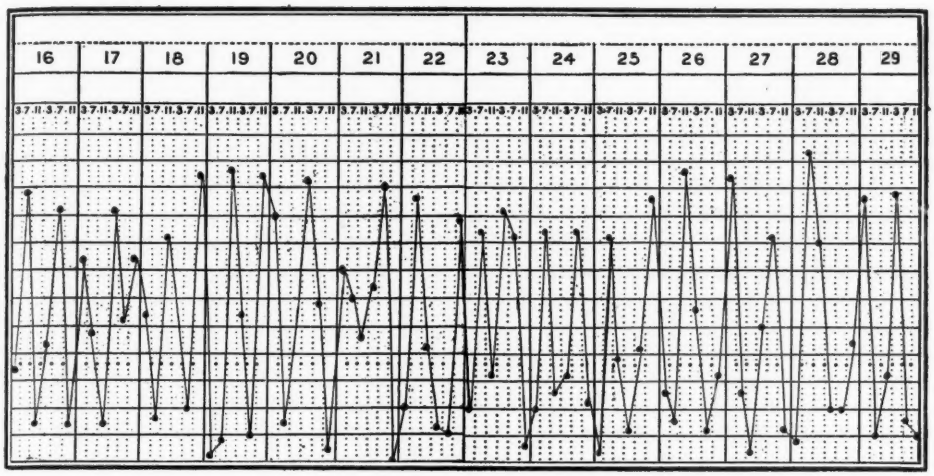



CHART 8. Showing fever during gonococcal endocarditis continued in Chart 9.

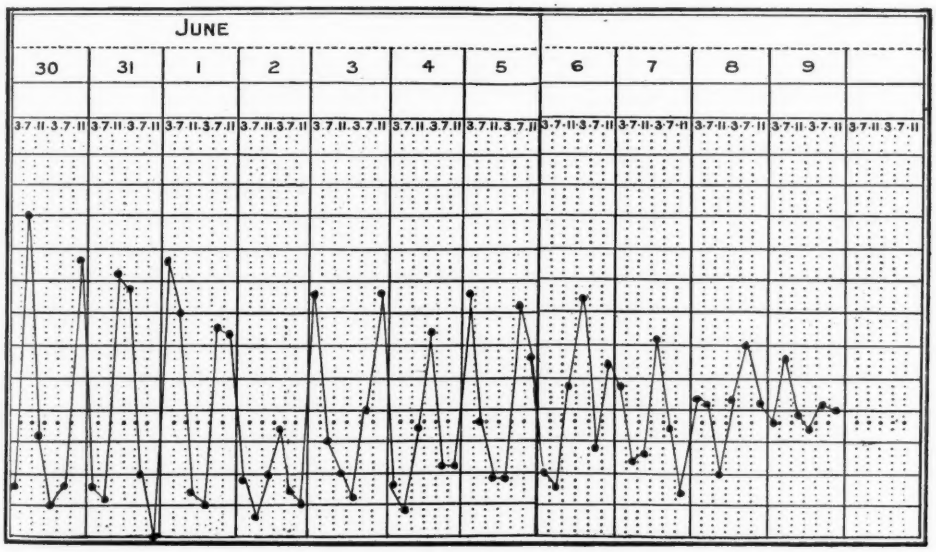



CHART 9. Showing the decline of the fever, in a case of gonococcal endocarditis, with the development of nephritis and uraemia.

though usually streptococcal, I have seen most marked anaemia also in pneumococcal and influenzal cases. All the microbes causing the disease are powerful haemolytic agents, the streptococci especially.

*Leucocytosis.* In the acute cases there is usually a fairly high leucocytosis, at least until a few days before death; figures of 20,000–30,000 are common. In the subacute and chronic cases, however, the rise in leucocytes is much more moderate; indeed, the absence of a high leucocyte count is a feature of many of the cases. Out of 46 cases of all forms of the disease in which leucocyte counts are recorded, the figures were less than 15,000 in 30. In a chronic case, streptococcal in nature, investigated by Dr. Thursfield ten separate counts showed figures always lying between 8,000 and 10,000. In Dr. Ormerod's gonococcal case, which was the first of such cases to be diagnosed by blood-culture in this country, I found the leucocyte counts to be as follows:—May 5, 22,000; May 17, 21,500; May 24, 12,000; May 27, 9,200; June 2, 9,200; June 8, 11,500; (June 9, death). The high early leucocytosis is thus seen to have gradually diminished with the patient's loss of resistance, a terminal increase occurring just before death.

(iii) *Loss of flesh.* Another common feature in the disease, occasionally progressing in the chronic cases to a degree of emaciation which, together with the anaemia, the fever, and the presence of valvular disease, forms a very characteristic clinical picture. The slow loss of flesh which attracts attention at the outset of the chronic cases has been referred to already.

(iv) *Pains*, either in the joints, or limbs, or back, or abdomen, are common. Reference has been made to the occurrence of tenderness and discoloration of the skin, and to the significance of these areas. A similar condition is sometimes present in the terminal phalanges of the hands or feet, in the heels, or elsewhere on the body. Pains in the joints were present in 66 of the cases at some time or other, and the joints were swollen in 22 cases. More often than not the pains are indefinite, both in situation and cause.

In a few cases intolerable 'lumbago' occurs, or pain may be referred to the spine. In one case I have seen intense sacralgia present. The abdominal pain, which is not infrequent, appears definitely attributable to perisplenitis in some cases; in others to the formation of small aneurysms in the mesenteric and other vessels; sometimes to rapid enlargement of the liver.

(v) *Albuminuria* was present in 54 cases, or about one-third. This is not including the cases of haematuria, a symptom dealt with under the section on embolism (page 306). In about half of the 54 cases there was evidence of nephritis; there was also evidence of nephritis in 18 out of the 46 cases showing haematuria. Thus, evidence of nephritis occurred in 45 out of 150 cases, or nearly one-third. It is undoubtedly a very common complication of the disease.

xiv. *Modes of Termination.* (*a*) *Recovery.* A rare event, yet one which certainly seems occasionally to occur, if it be conceded that a diagnosis may be made in the absence of one or more of the three cardinal signs above mentioned. Of the 150 cases upon which these remarks are based only one recovered. This was a boy, aged 15, under the care of Sir Dyce Duckworth at St. Bartholomew's Hospital in 1902. The onset of the disease was abrupt, with a rigor, pains all over, but no swelling of joints. The fever was quotidian intermittent (97°–105°),

and there was no response to full doses of sodium salicylate. There was a loud systolic murmur all over the heart, loudest at the apex. The heart was dilated. A papular erythema was present on the abdomen and legs, appearing and disappearing two or three times. A Widal test was negative. Rigors occurred almost daily. The spleen was not palpable, there were no signs of embolism, and two blood-cultures were both negative. 'Polyvalent' anti-streptococcus serum was given hypodermically in 10 c.c. doses upon each of two days without effect. When the fever had persisted unaltered for seven weeks 10 c.c. of the serum were given *per rectum* and continued daily. The temperature fell gradually to normal after the eighth dose, and remained normal. The boy got completely well, and lost all signs of cardiac disease.

(*b*) *Death* occurred in 141 cases; the remaining 8 cases discharged themselves from hospital, but were all so ill on leaving that it is extremely probable that the same event happened to these also. In 66 cases the terminal event was *circulatory failure*, usually with rapid dilatation of the heart and anasarca. In 23 cases the patient died *comatose*. In 19 cases death was *sudden*, and due to one or other of the accidents described in the section on embolism, or to changes of a destructive nature going on in the heart,—rupture of an aneurysmal dilatation of a valve, perforation of the interventricular septum or wall of the auricle or ventricle,—or to cerebral haemorrhage. In 18 cases the mode of termination was by *uraemia*, with renal oedema and suppression of urine. As already mentioned, nephritis was present before death in no less than a third of all the cases. In 8 cases the patients appeared to die of exhaustion, and in 5 from delirium and mania. Hyperpyrexia was present at death in 2 cases.

xv. *Diagnosis.* Many points connected with diagnosis are scattered over the foregoing account of the signs and symptoms of the disease. A few diseases which need to be distinguished from infective endocarditis are the following:—

(i) *From acute infective endocarditis.* (*a*) *Pneumonia.* The resemblance may be very close indeed. The pneumococcal cases generally accompany pneumonia, and the pulmonary disease is not seldom of an irregular character. Care must be exercised, for haematuria and splenic enlargement in a case of pneumonia do not necessarily imply infarction. Nor would a positive blood-culture necessarily point to endocarditis, for pneumococci may be isolated from the blood of many severe cases of pneumonia. Petechiae, however, and the plugging of arteries, in a case in which signs of valvular disease and a positive blood-culture were present, would justify a diagnosis being made.

(*b*) *Typhoid fever.* Great importance must be attached to the agglutination test, especially in conjunction with a leucocyte count: a positive Widal test with a leucopoenia may be regarded as almost decisive in favour of typhoid fever. Positive blood-cultures may often be obtained during the first week of typhoid fever, but a true typhoid infective endocarditis must be very rare.

(*c*) *Rheumatic fever.* It is probable that all the symptoms and signs of infective endocarditis may be met with in rheumatic fever, save the isolation of micro-organisms from the blood. Recurring attacks of subacute rheumatism

in patients who have previously developed valvular disease often give rise to considerable anxiety on account of the similarity which they bear to the symptoms of infection of the endocardium. Even when, in the genuine rheumatic cases, the arthritis yields to the administration of salicylates, there may still remain fever, acute endocarditis, inflammation of other serous membranes, enlarged spleen, skin eruptions, haematuria, and progressive anaemia; yet the case should not be regarded as necessarily very grave in the absence of positive blood-cultures on repeated trials.

(*d*) *Malaria* is closely simulated by some of the cases of infective endocarditis, as already remarked in connexion with the gonococcal cases. The patient may have had ague previously. The absence of the malarial parasite in the blood-films and the absence of a leucopoenia are valuable diagnostic facts in this connexion.

(ii) *From chronic infective endocarditis.* (*a*) *Prolonged attacks of subacute rheumatism* are again sometimes difficult to mark off satisfactorily from the disease. Occasionally the rheumatic process may spread itself over a period of several months. This, when it occurs, is usually seen in children between the years 10–16, less often in young adults. Endocarditis is always present, and often pericarditis or pleurisy, or both; relapses may occur with either of these complications. Chorea may appear, especially towards the end of the disease. Loss of flesh may be extreme. The form of fever is irregular and may show large oscillations which are spread over several days. Nodules may be present. Facts which help to exclude infection of the endocardium are the absence of petechiae, of haematuria, of a severe grade of anaemia, and, especially, of micro-organisms in the blood-stream. In one of these prolonged rheumatic cases, which ultimately recovered completely, next to the sterility of the blood on culture most assistance was derived from the absence of anaemia—a most significant finding, seeing that the illness had already lasted more than four months. In this case some support was given to the notion of infective endocarditis by good results following the use of anti-streptococcus serum; a change from the anti-serum to normal horse's serum was not followed by any such improvement. But a non-specific effect may be derived from anti-streptococcus serum in a variety of diseases.

(*b*) *Tuberculosis.* The combination of fever, however slight, with loss of flesh and strength, observed in so many of these cases, naturally raises the question of tuberculosis of some deep-seated organ, and especially of pulmonary phthisis. 'Phthisis without physical signs' was for some months the working hypothesis in a very protracted case that came under my notice and in which a blood-culture gave a growth of *staphylococcus albus.* Sometimes chronic cases of infective endocarditis find their way into sanatoria for the treatment of phthisis, a diagnosis of this latter disease being made on the above grounds.

xvi. *Prognosis.* Whatever doubts there may be as to the existence of occasional recoveries from the acute form of the disease, there seems little doubt that the chronic cases are invariably fatal. Indeed, of no disease except

inoperable cancer may it be said so confidently as of chronic infective endocarditis, that as soon as the diagnosis is made the patient's death-warrant is signed. That the patient is apparently very little affected in general health, that he is a robust-looking man, or that he has been singularly free from illnesses in the past (unless it be an attack of acute rheumatism many years ago) —none of these things may tempt the physician to abate anything from the seriousness of the case. Periods of apparent or of real improvement may follow certain lines of treatment, or may supervene without them, but the fatal issue seems only to be delayed. If the natural course of the disease is not completed, there are still to be reckoned with the various accidents that attend upon the dissemination of the endocardial vegetations or of the ulceration of the structures affected, either of which accidents may bring about a speedy termination. Even the efforts at cure would seem to bring grave risks in their path. For cure can only come through inhibition of the bacterial growth in the endocardium; if this growth be successfully coped with disintegration of the fungating vegetations is likely to occur, and this may mean fatal embolism. How to detach these thrombi in such a fine state of subdivision that no vessel of any conspicuous size is obstructed by the particles which are cast into the blood-stream is the therapeutic problem that faces us. The chief hope in regard to this would seem to lie in establishing the diagnosis at as early a date as possible so as to employ whatever measures promise success before the vegetations have attained any great size.

As regards the time a patient is likely to live after the disease has become manifest, it is often very difficult to surmise. If there are already present the signs of renal or cardiac failure the end is not far off. Otherwise developments may proceed quite slowly, and the patient may live several weeks or even months. In two of my cases the patients lived as long as four and five months respectively after a positive blood-culture; in six cases they have lived more than two months after thus confirming the diagnosis. The possibility of the accidents already alluded to must always be put before the patient's friends. No improvement in the general condition, not even improvement up to the point of bringing conviction that the particular treatment at the time is doing good, seems to confer immunity against these accidents. Not seldom, when it appears certain that the course of the disease has been checked, and the state of septicaemia is being successfully combated, death, more or less sudden, and due to some purely mechanical cause, cheats alike the physician and those who watch his efforts.

xvii. *Treatment.* (i) *Preventive.* I do not know that it has ever been suggested that measures should be taken to prevent this most serious disease. In cases of the primary form, where no previous valvular lesion has been present, no such prophylactic measures would be possible. But in the secondary form of the disease, where the infection is grafted upon a previously sclerosed endocardium, and which, as already said, includes by far the majority of the

cases, it is possible to do something to prevent the development of the mischief. Reference has been made to the undoubted fact that the source of the infecting agent in most of the cases is the mouth or intestine. This suggests that attention might profitably be directed to these regions in all persons known to possess valvular defects. 'Oral sepsis' should receive definite treatment, and, though the cause and effect are in this particular more difficult to trace, constipation should be avoided. Periodic administration of small doses of calomel or grey powder might conceivably reduce the tendency of intestinal streptococci to transgress the barriers which usually suffice to keep them outside the blood-stream. Whether or not a patient's susceptibility to invasion by these 'saprophytes' of the alimentary canal could be lowered by an occasional dose of vaccine prepared from a mixture of strains of salivary and faecal streptococci is a matter that also calls for investigation.

(ii) *Curative.* Over and above the general or non-specific measures in the treatment of the septicaemia which is an essential part of the disease, such as plenty of fresh air and light, good nourishing food, and remedies designed to combat the tendency to anaemia, there may be passed in review various specific measures for inhibiting the bacterial factor of the disease. These may be treated of under three heads: —

(*a*) *Chemical antidotes.* These have received abundant trial in the history of the disease, but have rarely if ever appeared successful. 'Blood antiseptics' seem doomed to failure in dealing with pyogenic blood infections because it is not possible to get the drugs into the blood in a nascent or active condition: combination with the proteids of the blood-cells or plasma takes place before the drug comes into direct contact with the micro-organism. Quinine, mercury, arsenic, carbolic acid, formalin, and many other reputed remedies, all fail, whether administered by mouth, subcutaneously, or intravenously. The sulphocarbolates, which have had a special vogue, are equally disappointing: I have used them in very large doses in several cases without any results. Silver salts in combination with nuclein have been highly spoken of in the treatment of septicaemia, but here again I have never seen any good results in infective endocarditis. The same remark applies to yeast and its active principle.

(*b*) *Anti-sera.* The introduction of anti-streptococcus serum, and especially of the 'polyvalent' serum, raised hopes in regard to the treatment of the disease, because of the frequency of the streptococcal cases. It must be conceded, however, that the results of its trial are very disappointing. Of 39 cases in my series that were treated in this way only one recovered—the boy under the care of Sir Dyce Duckworth, referred to on p. 316. In this case, unfortunately, no micro-organism was demonstrated in the blood. I have given the treatment most thorough trial in several cases, and have occasionally seen temporary improvement result, but never any permanent good. Chart 9 shows the effect of 30 c.c. of 'polyvalent' anti-streptococcus serum given daily to a case of the disease demonstrated to be streptococcal by blood-culture: a definite lysis occurred, to be soon followed by a return of the fever to its

original form, despite the continuance of the remedy. It is maintained by some authorities that harm may result from giving too much anti-serum, leading to the production of anti-antibody; but with this caution in mind the treatment is still almost barren of results.

An explanation of this failure of anti-serum may lie in the exceptional nature of the streptococci concerned in the disease, and in the fact that the anti-sera on the market are generally prepared from various strains of streptococcus pyogenes. A 'polyvalent' serum does not dispose of this difficulty, for to produce it streptococci from different disease processes are used rather than streptococci having known differences of reaction. It is doubtful, therefore, whether these sera can be expected to be potent against the faecal and salivary strains of streptococci found in the diseased endocardium. With the idea of overcoming this difficulty I have upon two occasions prepared a special anti-

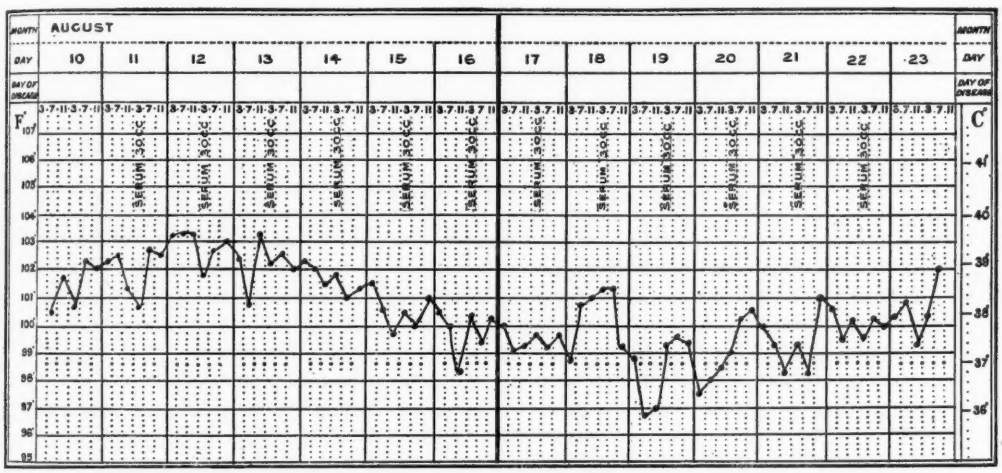



CHART 10. Showing a fall in temperature during the administration of anti-streptococcus serum, in a case of streptococcal endocarditis.

serum from the micro-organism actually isolated by blood-culture in cases of infective endocarditis. In the first of these cases there seemed ample time both for preparation of the serum and for trial of it; yet no satisfactory result followed (*Lancet*, July 16, 1904). In the second case the patient was very ill at the time the special serum was forthcoming. Seeing that it takes at least a month to prepare an anti-serum that can hold out any promise of being rich in antibody, this method of treatment by special sera is obviously impracticable as a general means of combating the disease. If, however, a number of the strains of streptococci found in cases of infective endocarditis were used for inoculation into the horse, or if the salivary types and the faecal types were used in each of two horses respectively, a stock serum would be available for trial as soon as the nature of the streptococcus in any case was known. This suggestion was recently made by Andrewes and myself in a paper dealing with the pathogenic

streptococci. Until it has been carried out it cannot be said that the treatment of the disease by anti-sera should be abandoned as useless. Finally, the mode of administration of the serum may be important; it may be that it would act more beneficially if introduced directly into the blood by intravenous injection. Analogy with the good effects recently obtained by the intraspinal use of anti-meningococcus serum in cerebro-spinal meningitis suggests this. In one instance—a case of pneumococcus endocarditis, treated by Pane's serum—in which I gave the serum intravenously, some considerable improvement followed for a time. In three other pneumococcus cases, treated subcutaneously, no improvement was seen (*Lancet*, June 4, 1904, and May 20, 1905).

(*c*) *Inoculation.* The hopes of cure which were entertained on account of serum treatment had drooped considerably when they revived at the adaptation by Wright of the principle of specific inoculation to the treatment of pyogenic infections. The experience of this latest phase in our efforts at combating the disease, however, cannot be said to be much more cheering than that of the one immediately preceding it. It is doubtful if a genuine instance of the disease has really been permanently cured by the employment of bacterial vaccines. One such case has been published by Barr, Bell, and Douglas conjointly, but from the record of the case the evidence of an infective heart lesion does not seem very convincing: the signs described may well have been due to a temporary dilatation of the right heart associated with tricuspid incompetence, a not uncommon condition in cases of septicaemia. In *The Practitioner* for May, 1908, I instanced a case of influenzal endocarditis, diagnosed by blood-culture, in which vaccine treatment seemed to produce a marked effect—gain in weight and colour, considerable diminution in the fever, and a sterile blood-culture. But I have now to record a relapse in this patient, and a fatal issue despite a third course of vaccine treatment. Wright and his pupils record two cases of streptococcal endocarditis which made no response to the treatment. My own experience embraces six streptococcal cases, all of which have died. In two, some amelioration of the general symptoms and of the fever appeared to follow the treatment, but there was no permanent improvement. In three of the cases frequent opsonic estimations were undertaken, but these did not seem to help in the choice of dose or in the frequency of its administration. In one case, in which the opsonic estimations were kindly undertaken for me by Dr. M. H. Gordon, the index rose to 3·0 at a time when the patient was manifestly losing ground fast, thus demonstrating the fact that the index was no guide to the state of immunity as a whole. I have seen these high opsonic indices several times in infective endocarditis. In the last streptococcal case which I have treated by vaccine, Mr. Girling Ball undertook daily opsonic counts independently of my inoculations, which were determined by the clinical conditions. The patient's disease certainly appeared to progress less rapidly during the treatment, but was none the less fatal in the long run, and here again the opsonic index rose steadily to a point slightly above normal before death. When the record of the indices and of the inoculations came to be compared they stood as follows:—

| *Date.* | *Opsonic Index.* | *Inoculation.* |
|---|---|---|
| July 26 | ? | 10 million cocci |
| 27 | 0·4 | |
| 28 | 0·6 | |
| 29 | 0·5 | |
| 30 | 0·56 | 10 million cocci |
| 31 | 0·5 | |
| Aug. 1 | 0·43 | |
| 2 | 0·72 | 20 million cocci |
| 3 | 0·38 | |
| 4 | 0·38 | |
| 5 | 0·78 | |
| 6 | 0·94 | |
| 7 | 0·97 | 20 million cocci |
| 8 | 0·74 | |
| 9 | 0·82 | |
| 10 | 0·82 | 20 million cocci |
| 11 | 0·69 | |
| 12 | 0·89 | |
| 13 | 0·9 | |
| 14 | 1·04 | 20 million cocci |
| 15 | ? | |
| 16 | ? | |

Of the 150 cases in my present series, 12 were treated by vaccines, but with no recovery. These cases include, besides the 7 already mentioned, one streptococcal case under the care of Dr. Norman Moore, one under the care of Dr. Ormerod, two under the care of Dr. Herringham, and one gonococcal case under the care of Dr. Herringham.

With such despondent results of vaccine treatment, the hope of establishing some process of cure for these cases of endocardial infection languishes once more. Yet with a disease-process so localized, and with its etiological factors so well understood, a rational system of successful treatment may still be looked for. The prospect is so dismal in the case of any patient suffering from the disease, especially in its chronic form, that some boldness in treatment is demanded, and will probably be necessary before cures are effected. At present it seems clear that specific inoculation should be given an extended trial in every case, and that this effort at active immunization should be accompanied by the use of bactericidal sera, specially prepared. Two immediate suggestions that may be made as the result of the failure of both these methods up to date are that the bacterial vaccines should perhaps be given up to the point of obtaining local, or even slight general, reaction, and that the anti-sera should be tried by the venous route. As a non-specific measure a rigid open-air regimen might be added.

For kind permission to make use of the records of cases under their care, my thanks are offered to the physicians at St. Bartholomew's Hospital and to my colleagues at the Great Northern Hospital. My acknowledgements are due to the Museum Committee of St. Bartholomew's Hospital for permission to photograph several specimens. For much of the statistical matter included in this paper I have to thank my house-physician, Mr. Gow.

## DESCRIPTION OF PLATES.

### PLATE 17 (Coloured).

The kidneys from a case of influenzal endocarditis, in a man aged 37. The disease lasted six months. Subcapsular haemorrhages are seen in large numbers. The kidney substance is pale. Two or three old infarcts are present. The appearances are those commonly seen in subacute or chronic cases of infective endocarditis.

### PLATE 18.

FIG. 1. Infective endocarditis; aortic; showing two aortic cusps only; on one of these is a patch of vegetations, the proximal portion of which has ulcerated and has led to perforation of the cusp. (From a specimen in the Great Northern Hospital Museum.)

FIG. 2. Infective endocarditis; mitral; showing perforation of a mitral cusp. (From a specimen in the Great Northern Hospital Museum.)

FIG. 3. Infective endocarditis; mitral; showing the valve orifice blocked by a single mass of vegetations. (From specimen no. 1327 in St. Bartholomew's Hospital Museum.)

FIG. 4. Colon bacillus endocarditis; aortic; showing large isolated masses of vegetations, pedunculated. (From specimen 1299 h in St. Bartholomew's Hospital Museum.)

FIG. 5. Pneumococcal endocarditis; mitral; showing partial obstruction of mitral orifice by vegetations, and extension on to wall of auricle. (From specimen 1316 in St. Bartholomew's Hospital Museum.)

FIG. 6. Staphylococcal endocarditis; showing mural auricular endocarditis due to *S. albus*, without involvement of mitral cusps.

### PLATE 19.

FIGS. 7 AND 8. Pneumococcal endocarditis grafted on to a heart which is the seat of congenital defects. In Fig. 7 the aortic cusps are seen to be thin and primarily involved by large vegetations. In Fig. 8 a large area of the wall of the pulmonary artery remote from the aorta is seen to be covered by small vegetations which have spread downwards from a patent ductus arteriosus. The pulmonary cusps are natural.

FIGS. 9 AND 10. Streptococcal endocarditis grafted on to a congenitally diseased heart. In Fig. 9 the aortic cusps are seen to be affected by the disease; the patent interventricular septum is also seen. In Fig. 10 a triangular area, covered by vegetations, is seen spreading directly from the hole in the septum (seen to the right) on to the wall of the right ventricle. (From specimen 1299 $e_2$ in St. Bartholomew's Hospital Museum.)

FIG. 11. Gonococcal endocarditis; aortic; illustrating primary infection of a previously healthy heart; a thin and flexible aortic cusp is seen between the vegetations.

FIG. 12. Pneumococcal endocarditis; tricuspid; showing the enormous lumpy vegetations which sometimes occur in this variety of the disease. (From specimen 1312 in St. Bartholomew's Hospital Museum.)

### PLATES 20 AND 21.

FIG. 13. Infective endocarditis involving an abnormal aortic valve which consists of two cusps only; showing the marked sclerosis which previously affected these cusps and the base of the aorta.

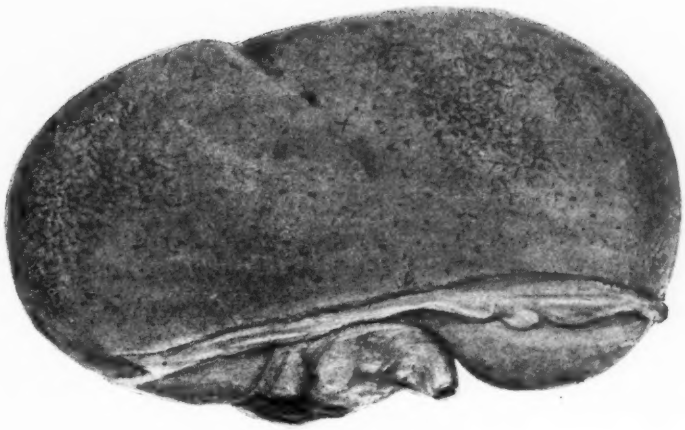
FIG. 14. Infective endocarditis; showing perforation of an aneurysm of a mitral valve cusp. (From specimen 1354 in St. Bartholomew's Hospital Museum.)

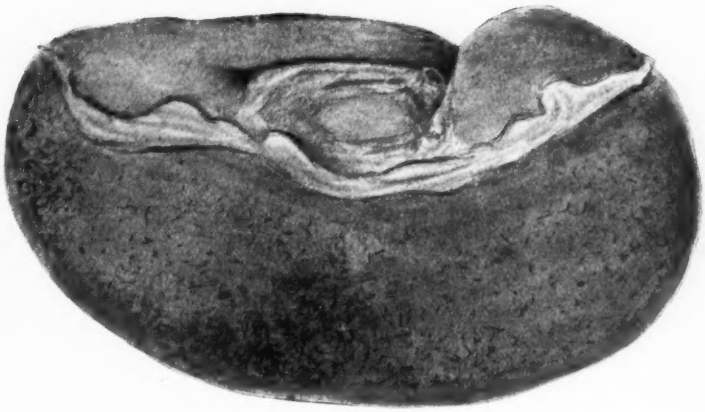
FIGS. 15 AND 16. Influenzal endocarditis. Fig. 15 shows a single sessile mass of vegetation situated on the wall of the left auricle. Fig. 16 shows extension of the infection through the base of the mitral cusp on to the ventricular surface. There is very great hypertrophy of the left ventricle, due to the presence of only two aortic cusps, which are sclerosed and rolled up, causing aortic regurgitation. (From specimen 1301 a in St. Bartholomew's Hospital Museum.)

FIGS. 17 AND 18. Blood-broth tubes illustrating the growth of colonies of influenza bacilli from a case of influenzal endocarditis. In Fig. 17 a few colonies only are seen; in Fig. 18 a very large number.

FIG. 19. A section ($\times 50$) taken through a mitral cusp infected by influenza bacilli.

FIG. 20. Three rabbits' hearts; showing the lesions of infective endocarditis produced by intravenous injection (1) of streptococci derived from the blood of a patient suffering from infective endocarditis; (2) of streptococci derived from normal human saliva; and (3) of streptococci derived from normal human faeces. (From 'A Report on the Micro-organisms of Rheumatic Fever and Malignant Endocarditis', *Local Government Board Reports*, 1906-7. Reproduced by permission of the Local Government Board.)





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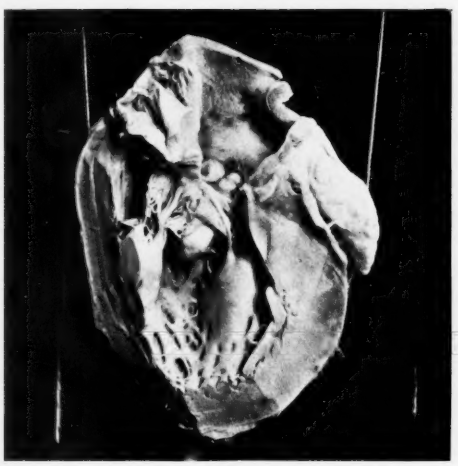

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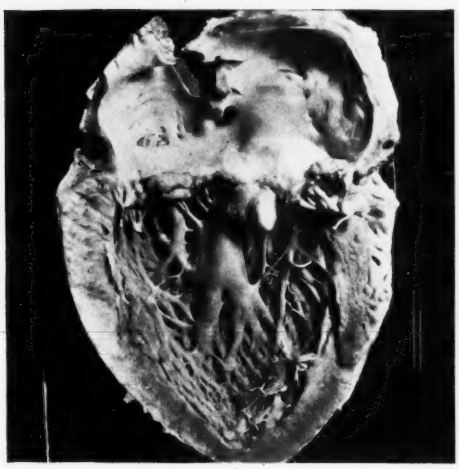

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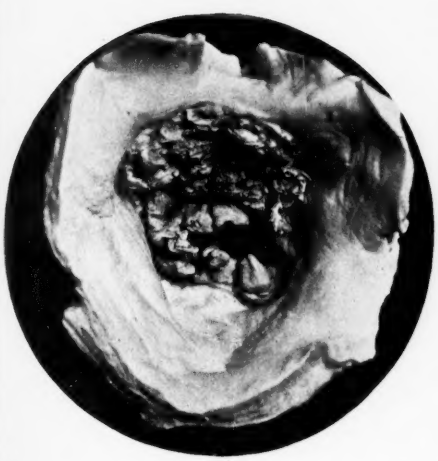

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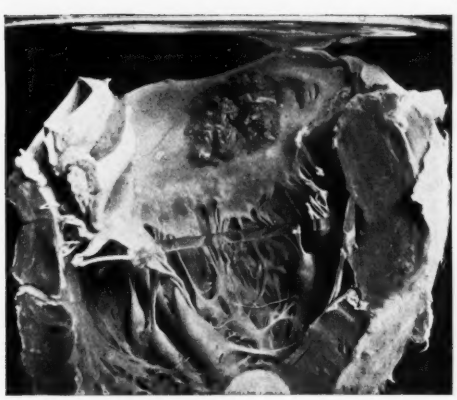

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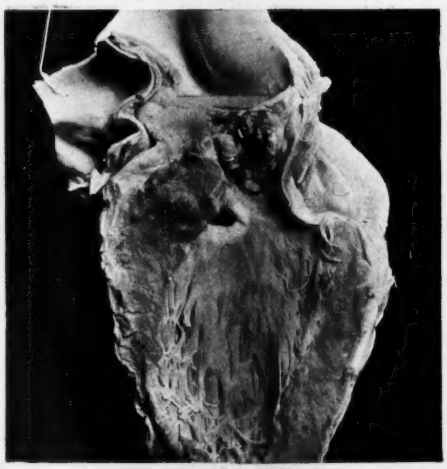

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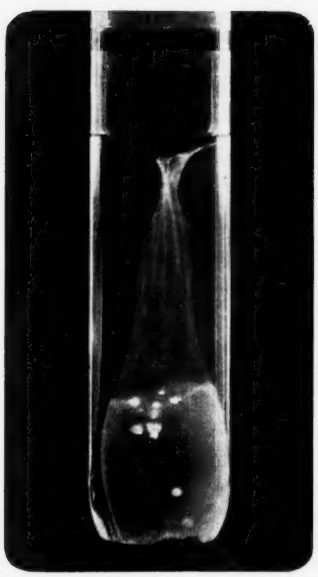

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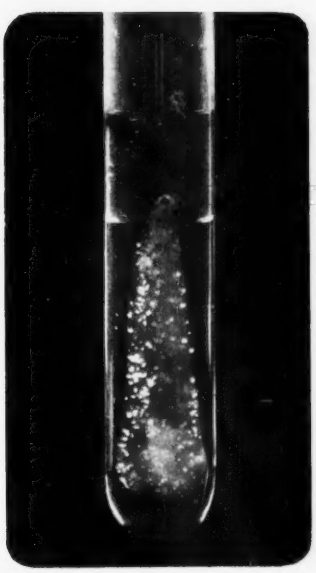

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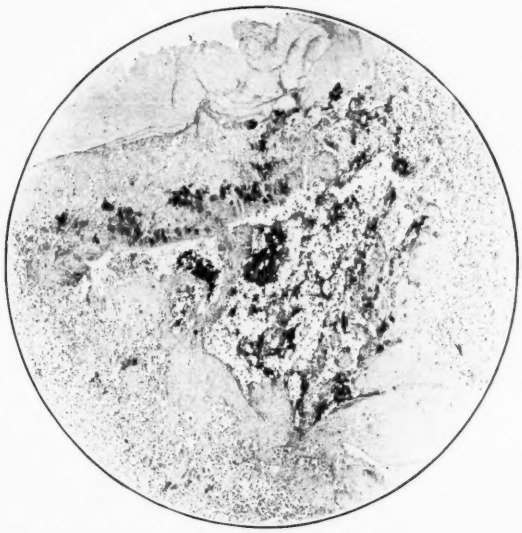

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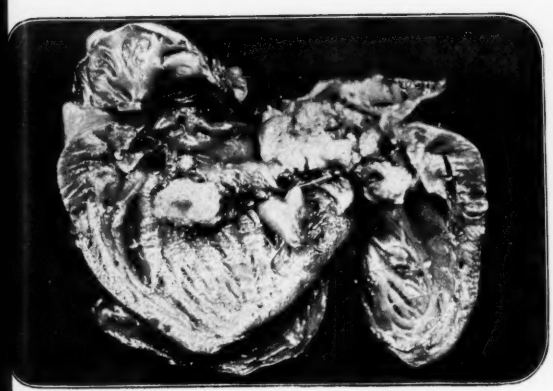

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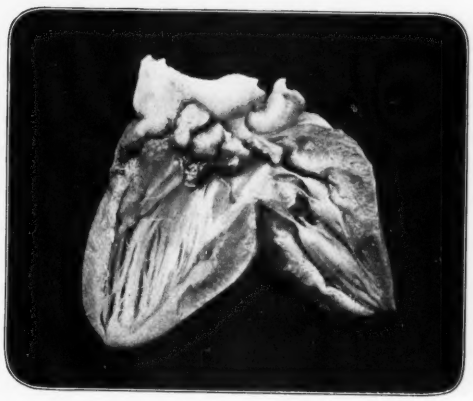

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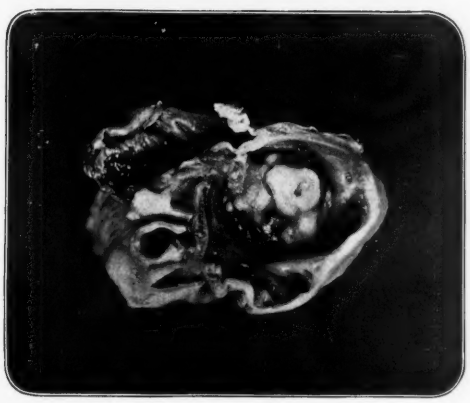

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# CRITICAL REVIEW

## ACIDOSIS

By EDMUND I. SPRIGGS

### Part I

The healthy performance of the functions of the tissues depends upon chemical and physico-chemical processes taking place in solutions of a certain composition. The balance between the acid and basic ions of the tissue fluids is held slightly in favour of the latter, so that the chemical reaction is faintly alkaline. Any disturbance in metabolism which tends to reverse this condition, that is, tends to diminish the alkalinity of the juices, may set up a state of *acidosis*. Such a disturbance does not necessarily lead to an actual reduction of the alkalinity, at all events of those fluids which are obtainable for chemical examination, since the body is possessed of means of defence against such a gross alteration of the composition of its more essential parts. Indeed, considerable quantities of acid may be taken by the mouth, or may be produced in the body by abnormal metabolic processes, and yet lead to no appreciable alteration in the reaction of the tissues or the blood, being combined rapidly with alkali and passed out in the urine. The neutralizing base is of two kinds: first, the sodium in the body fluids, potassium in cells, and the alkaline earths, derived chiefly from the bones; secondly, ammonia produced from the hydrolysis of protein, the bulk of which would, in the absence of the call for alkali, have been converted to urea and excreted in that form. If the amount of acid ingested or produced in the body be so great that it cannot be neutralized in either of these ways, or disposed of by oxidation, then the reaction of the tissue fluids can no longer remain unaltered, and there is danger of the symptoms of *acid intoxication* setting in.

Acidosis, then, is characterized by the excretion in the urine of an excess of acid radicles. These may or may not be those normally present. In the forms of acidosis most commonly met with in disease, organic acids are found which are foreign to healthy urine. A rise in the acidity of the urine is not a necessary consequence of an excess of acid radicles; indeed, if the mechanism mentioned above for the neutralization of acid were complete, the reaction of the urine would be unaffected, as all acids would be passed out as salts or esters. It commonly happens, however, that the alkali provided by the body is insufficient for complete neutralization, with the result that the acidity of the urine is raised.

[Q. J. M., April, 1909.]

Excess of acid may be produced in the body long before any appreciable reduction in the alkalinity of the blood is found. In other words, acidosis may exist for a great length of time without passing into acid intoxication. The reservation of the term acid intoxication for the latest stage of all, in which severe and commonly fatal symptoms arise, is not entirely satisfactory, for clinically there is no definite dividing line between the two conditions; it is clear that as soon as the alkaline reaction of the blood is constantly lowered the mechanism for the neutralization and excretion of an excess of acid has begun to fail, though unequivocal symptoms of intoxication may not have appeared.

In the present state of our knowledge, five tests may be mentioned by which the presence of acidosis may be determined.

The first has already been referred to, namely, the presence of an excess of acids in the urine. With this may be coupled, as will be seen later, the second, namely, the presence of acetone in the urine or breath.

The third is the reaction to alkali. If about 8 grammes (2 drachms) of sodium bicarbonate be dissolved in water or milk and taken by the mouth, the urine in a normal individual will become alkaline and remain so for about twenty-four hours. But in a patient who is producing an excess of acid in the body, the soda will combine with the acid radicles to be passed out in the form of neutral salts, and will fail to alkalize the urine. This may be seen in any severe case of diabetes, and the amount of sodium bicarbonate which may be taken without producing neutrality or alkalinity of the urine may be regarded as a measure of the degree of acid production.

The fourth test is the reduction of the alkalinity of the blood. When this test is positive, there is danger of the condition passing from one of acidosis to one of acid intoxication.

Fifthly, a valuable indication of the presence and degree of acid poisoning is afforded by the amount of ammonia in the urine.

*Poisoning by mineral acids.* The simplest form of acid poisoning is that induced by the experimental administration of mineral acids. Walter, in 1877, found that if more than 0·7 to 0·8 gramme per kilo of hydrochloric acid was placed in the stomach of rabbits in 0·4 or 0·8 per cent. solution, in three doses in twenty-four hours, there followed a rapid pulse, deep breathing, and loss of muscular power, ending in death. The alkalinity of the blood was reduced though not abolished—that is to say, death occurs before the blood can become acid to litmus. The volume of carbon dioxide that could be extracted from the blood sank from 32 to 2 to 3 volumes of gas per 100 volumes of blood. It has been supposed that in acid poisoning the blood can no longer carry carbon dioxide from the tissues to the lungs because its soda is taken into combination with the acid administered. We shall see, however, that there is some experimental evidence against this explanation. Walter showed that the symptoms and fatal effects could be obviated by introducing alkali into the body. Thus three times the fatal dose of acid produced no symptoms, if an equivalent

quantity of sodium carbonate in 5 per cent. solution were injected under the skin. Further, in two rabbits poisoned with acid and in the stage of deep breathing which in the other animals only preceded death by about a quarter of an hour, the injection of a corresponding amount of sodium carbonate into the jugular vein resulted in complete recovery. In one animal which was apparently dead a resuscitation took place, but an hour later the symptoms recurred, and a second injection was useless.

The carnivora have a greater power of resistance to acids, their food consisting of acid-producing material, and containing comparatively little base. Walter gave twice as much acid to dogs as to rabbits with much less effect. In these animals the ammonia in the urine rose from a normal 0·57 gramme to an average of 1·3 grammes per day. When acid was given on one day the excretion of ammonia remained high for the following day. Thus in one experiment, on two control days 0·7 gramme per day were passed out, on the acid day 1·8 grammes, and on the two following days, 1·2, 0·8 and 0·6 grammes. The ammonia passed out sufficed to neutralize about 75 per cent. of the acid administered; the remainder would be, most of it, accounted for by fixed bases. Miquel had shown in 1851 that the alkali in the urine was increased when mineral acids were given. Jaquet also found that the effects of mineral-acid poisoning were much less marked in dogs than in rabbits. He demonstrated in a striking manner that the alkalinity of the blood was little affected by the introduction of relatively large amounts of acid. For instance, after the injection of enough hydrochloric acid into a vein to neutralize all the blood, its alkalinity was only reduced by 4 to 7 per cent., a reduction less than the mere dilution with fluid would cause. It is evident that alkali must have been furnished in considerable quantity from the tissues, and we may deduce from such results that if, in disease, the blood be found to have suffered a considerable diminution in its alkalinity, then the rest of the body has suffered to a greater extent. Since the mineral acid was eliminated by the kidney chiefly in combination with ammonia, presumably the ammonia derived from amino-acids formed in the metabolism of protein is intercepted by acid molecules present in the body in excess and passed out without being turned to urea. Ammonia was not, however, found to be in excess in the blood, and from this it was assumed that the acid in the blood was bound to fixed alkali and only transferred to ammonia in the final act of excretion.

The dyspnoea produced in dogs was attributed by Jaquet to the action of the neutralized acid upon the nerve centres. It does not follow, however, as has been indicated above, that because the acid is neutralized in the blood, it is neutralized to the same degree in the tissues; on the contrary, it is probable that the tissues suffer long before the blood shows any change. Further, large quantities of neutral salts can be taken without being followed by these symptoms.

Dunlop investigated the effect of the administration of large doses of dilute mineral acids in man; 6 drachms (21 c.c.) of the dilute hydrochloric or sulphuric acid of the British Pharmacopoeia were given daily for two or for three

days and the urine analysed in this period and for control days before and after. The diet was a constant one during the observations. The analyses showed in an interesting manner the increase in the excretion of ammonium, sodium, and potassium in the urine, observed in animals by the workers referred to above. The three bases added together were nearly sufficient to neutralize the acid given. For instance acid equivalent to 68·8 c.c. of a normal solution was taken, and led to an increase of the three above-mentioned bases in the urine in a quantity equal to 55·3 c.c. of normal solution; calcium and magnesium were not estimated.

The *deprivation of mineral salts* is followed by a depletion of the body of bases with a corresponding excess of acid. The metabolism of protein results in the formation of acid products, sulphuric and phosphoric acid, from its sulphur and phosphorus, and the excretion of these as salts carries out a proportion of the fixed bases of the body. Consequently the urine continues to pass out mineral salt although little or none is taken by the mouth, and the net result is a loss of base. Lunin showed that in mice upon a salt-free diet life could be prolonged from an average of 21 to about 36 days by the addition to the food of an amount of sodium carbonate equivalent to the estimated production of acid from the oxidation of protein.

But neither want of base nor want of crude mineral matter in general is the sole cause of the death of animals fed upon a diet freed from salts, for it was found that animals fed on salt-freed casein and lactose, although their lives were prolonged if an equivalent quantity of the original salts or of sodium carbonate were added, ultimately died, whilst they could live indefinitely upon desiccated milk. It appears, therefore, that some inorganic material must be provided in its natural form of combination with protein food.

The occurrence of the '*relative acidosis*' said to be caused by *loss of alkali* from the body in diarrhoea cannot be regarded as proven.

*Acidosis upon a diet consisting of protein and fat, and during a fasting period.* We have seen that the metabolism of protein results in the depletion of the body of bases. In an ordinary mixed diet the vegetables contain a large proportion of salts, and these, especially the carbonates, citrates, and other organic acids, which act as bases in the body, make up the deficiency. If no vegetables are taken, however, the loss may result, in an omnivorous animal, in a condition of acidosis, if ammonia is not formed in sufficient degree entirely to protect the fixed bases. During fasting similar conditions obtain, since the body is living upon its own store of protein and fat. Hence a protein and fat diet, or starvation, unless a sufficient amount of the appropriate mineral matters is specially provided, may result in acidosis, even when we look to the metabolism of inorganic salts alone.

The withdrawal of vegetable food, however, besides involving a loss of salts involves the withdrawal of carbohydrate; this is of great importance, for in man the absence of carbohydrate from the diet may be followed, both in health and disease, by the appearance of certain organic substances in the urine—acetone,

diacetic acid, and oxybutyric acid. These are of more importance in the practical consideration of acidosis than any other bodies. It is true that the first named, acetone, is not an acid body, as it belongs to the class of ketones. It is, however, derived from oxybutyric and diacetic acids, and thus even when it alone, of the three bodies, is found in the urine, its presence is indicative of an abnormal production of organic acids in the body.

We must, therefore, consider as briefly as possible the properties and the metabolism of oxybutyric acid, diacetic acid and acetone; again emphasizing the fact, not yet sufficiently appreciated by the bulk of the profession, that they may be formed in the healthy body whenever the need for carbohydrate food is unsatisfied for a sufficient period; their presence cannot, therefore, be attributed to disease or inadequacy of any particular organ.

### *The Acetone Bodies.*

*β-oxybutyric acid*, $CH_3—CHOH—CH_2—COOH$, is the mother substance which, in the acidosis caused by the acetone bodies, gives rise to diacetic or aceto-acetic acid, $CH_3—CO—CH_2—COOH$, and acetone, $CH_3—CO—CH_3$. Oxybutyric acid has not been found in healthy urine; in a normal individual upon an ordinary diet a fair quantity of oxybutyric acid, when given by the mouth, can be oxidized with ease, without the appearance of diacetic acid or acetone in the urine; but in diabetes the oxidation fails, as it does in animals deprived of the pancreas, or poisoned with phloridzin, or with carbon monoxide, or fed exclusively upon fats. Its incomplete combustion in these conditions must be ascribed to a failure of some particular oxidative process and not to a want of oxygen. Since the acid can be dealt with by the healthy organism, and since the beta oxidation by which it is formed is one that can take place in the body, it is possible that it may be a normal intermediate product and one of the usual links in the metabolic chain of transformations, for the major part hidden from us, along which the food materials pass to their final excretory products.

Oxybutyric acid is usually recognized in the urine by its laevo-rotatory power, after any sugar present has been fermented. This method is not entirely satisfactory. When the acid is quantitatively estimated by a similar method or by deducting the observed rotatory power of a diabetic urine from that calculated from the amount of dextrose present the results are wholly unreliable, as Pembrey, Beddard, and myself found in a series of observations. The acid may be dissolved out from the urine in ether and weighed, or its rotatory power determined (Magnus-Levy); but probably the best way of estimating it is that described by Ryffel, in which the polarimeter is not used. This method gives accurate results with sodium oxybutyrate.

*Diacetic or aceto-acetic acid* appears in the urine when oxybutyric acid is ingested under the circumstances mentioned in the last section, though not in health. It has not been made directly from β-oxybutyric acid in the laboratory, but is formed when ammonium butyrate is treated with peroxide of hydrogen. It may, therefore, be regarded as a derivative of β-oxybutyric acid and not as an

independent product. When given by the mouth it is, in health, completely oxidized, probably by way of acetic acid; but in acidosis, it forms acetone. In the laboratory it breaks up into acetone and carbon dioxide with ease, when heated or boiled with dilute acid or alkali.

The amount of diacetic acid in the urine may be roughly gauged by the depth of the claret colour produced in the ferric chloride test. Its quantitative estimation is usually made by converting it into acetone and estimating the acetone so formed, together with that preformed in the urine, as iodoform, by the method of Huppert and Messinger, which requires great care, but is susceptible of considerable accuracy.

*Acetone* occurs in the urine in the less severe cases of acidosis, in which the oxidation of oxybutyric and diacetic acids is complete. When given by the mouth it is not oxidized so easily as its precursors, and being a volatile substance is passed out by the lungs as well as by the kidneys. It is found in small quantities in normal urine. Its characteristic sweet odour in the breath is often a means of diagnosis of diabetes and other forms of acidosis or acid intoxication. If more than half a gramme of acetone is present in the urine, diacetic acid is usually found, and if more than one gramme of acetone, $\beta$-oxybutyric acid as well. Any large amount of acetone bodies consists mainly of $\beta$-oxybutyric acid.

The acetone bodies are found in the urine in a large number of *clinical conditions*, of which the chief are diabetes, gastro-intestinal and liver diseases, fevers, many other diseases accompanied by progressive inanition, and after anaesthesia. In these, with the exception of diabetes, there is some degree of starvation involving the absence of carbohydrate foods. In diabetes there is more or less inability to make use of carbohydrates. The result in each case is that the individual is forced to supply his energy needs from protein and fat. In looking, therefore, for the source of the acetone bodies attention has been directed to these food-stuffs.

Butyric acid is one of the lower fatty acids, and since it is probable that the fat used by the body, either from the food or from its own stores, after being elaborated in the liver, is broken up into smaller molecules in the process of oxidation, it is easy to suppose that oxybutyric acid is derived from the imperfect combustion of some of these smaller molecules. According to current knowledge of the oxidation of fats, one molecule of butyric acid would be derived from one molecule of a higher fat. Leathes's view (38) is that that molecule would naturally be oxidized to carbon dioxide and water through the stages of diacetic and acetic acid, but that if, through some alteration of the normal process such as might be brought about by an excessive demand for the oxidation of fat, acetone is formed instead of acetic acid, then the occurrence of this abnormal step in the chain might result in the accumulation in the body of the preceding stages, namely, those of diacetic acid and $\beta$-oxybutyric acid.

It is known that in starvation from any cause great demands are made upon the fat stores of the body. In the first six days of fasting in man it has been

found that four-fifths of the total energy expended is furnished by the body fat. In this condition the liver becomes loaded with fat, which apparently undergoes some transformation in that organ before being oxidized.

If fat is the source of the acetone bodies, an addition of fat to the diet of a person, the subject of acetonuria, should favour the excretion of acetone; this has been found to be the case, and especially if the lower fatty acids, such as butyric, are added. If in starvation the higher fatty acids are given the total of the acetone bodies is not always increased. This has been explained by supposing that the added palmitin, stearin, and olein take the place of an equivalent quantity of body fat, and therefore the amount of fat oxidized is unaltered. The provision of energy in another form, such as that of protein, which would spare fat, is followed by a definite lessening of the acetonuria. The quantity of acetone bodies which may be passed out both in adults and children existing on fat and protein is considerable. In the case of a man who fed upon fat with a little wine for five days the amounts of $\beta$-oxybutyric acid, diacetic acid, and acetone in the urine were equivalent to those passed out in severe diabetes (35).

The ingestion of carbohydrate is followed by a rapid diminution in the excretion of acetone bodies, unless, as in severe diabetes, it cannot be used. 100–150 grammes, and in some cases even 50–60 grammes, are sufficient to abolish acetonuria in a few days in individuals who are starving or feeding entirely on protein and fat. The conclusion at once presents itself, that the carbohydrate spares fat, and, by lessening the amount used, reduces the strain upon the oxidizing powers of the body for fat. This is, no doubt, true so far as it goes, but it is perhaps not all the truth. For the quantity of carbohydrate sufficient to abolish oxybutyric acid and diacetic acid and acetone from the urine does not furnish so much energy as in such cases is being provided by fat. It is therefore suggested that carbohydrate food has some other function in aiding the oxidation of fat, such, for example, as to supply an easily assimilable nutriment to the liver cells, which are overworked by the increased fat metabolism.

A carnivorous animal, the dog, is not the subject of acetonuria either normally or in starvation, though he may become so in phloridzin or pancreatic diabetes; he is accustomed to oxidize much fat, and can probably make his own carbohydrate from protein (or fat) with greater ease than an animal used to take starch or sugar in its daily food. It would be interesting to know whether a pup receiving lactose in its milk suffers from acetonuria when taken from its mother. Even in mankind there are degrees of susceptibility to diaceturia; children showing it more rapidly than women, and women than men (30) (55). Indeed, there is not necessarily any appearance of acetone bodies in man in starvation; and especially if the body is depleted of fat (6). Halpern has recorded the case of a man with oesophageal stricture whose only food for twenty-six days is stated to have been 30 grammes of grape sugar per rectum, and whose urine contained no acetone or diacetic acid, and only 3·5 per cent. of the nitrogen in the form of ammonia.

Some other substances besides starches and sugar diminish or abolish the acetonuria of starvation; such are tartaric and citric acids (59). Citric and glutaric acids have been found to act in the same way in phloridzin glycosuria by Baer and Blum, and in diabetes by Bainbridge and Hurtley. Baer and Blum have also recently found that higher acids homologous with glutaric acid, and containing 6, 7 and 8 carbon atoms, produce this effect. Hirschfeld found that neither caramel, nor levulinic acid, nor alcohol had any effect in diminishing acetonuria. The last-named result is of importance since alcohol is commonly prescribed for diabetes: so far as this result goes, it appears that we cannot expect it to take the place of carbohydrate in facilitating the oxidation of fat, and thereby lessening acidosis.

It is possible that $\beta$-oxybutyric acid may be formed from either carbohydrate or protein. It seems improbable that carbohydrate helps in its formation, or at all events in its appearance as an abnormal product. In the case of protein, Embden has called attention to the derivation in the laboratory of acetone from leucin. Evidence has also been obtained that the surviving liver has the power of forming acetone from leucin. Leucin has also been found to increase the formation of acetone and of $\beta$-oxybutyric acid in carbohydrate starvation as well as in diabetes (Baer and Blum). Embden and v. Noorden point out that acetone from leucin might be a by-product in the formation of carbohydrate from protein, a process which we should expect to occur when carbohydrate was deficient in the food. The structure of oxybutyric acid and its derivatives is compatible with their formation from the simple fatty acids which would result from the desamidation of the amino-acids; it has not been shown, however, that this is likely to account for any considerable proportion of the acetone bodies. There is no correspondence between the rate of protein destruction and the amount of acetone bodies. Thus in early starvation the excretion of nitrogen is diminishing whilst the acetonuria is increasing (Leathes). An addition of protein to the diet has often been observed to lessen the excretion of acetone bodies in the urine, as is mentioned above.

*Lactic acid.* After the mineral acids, and oxybutyric and diacetic acids, lactic acid has most often been mentioned as the cause of acidosis. Lactic acid is probably a normal intermediate metabolic product, and is formed in muscle under experimental conditions. Hopkins and Fletcher showed that if the muscle was well supplied with oxygen no lactic acid appeared. We may, therefore, suppose that in health its oxidation is complete. When a special strain is put upon the nutrition of muscles, and oxidation is likely to be incomplete, as in severe muscular exercise, an epileptic fit, eclampsia, trichiniasis, and uraemia, lactic acid appears in the urine, and the alkalinity of the blood may be definitely depressed. The acid is not known to be harmful under such conditions; indeed a larger quantity than is found in them may be injected into the blood with impunity.

Lactic acid is also found in the urine when the liver has been excised (in geese), in acute yellow atrophy, phosphorus poisoning, and occasionally in cases

of extreme cirrhosis of the liver. But a very considerable destruction of liver substance, as in many liver diseases, and in experimental injury by hydrazine poisoning, or interference with its functions, as in Eck's fistula, may be present without the appearance of lactic acid. For this reason it has been suggested that when lactic acid appears in the urine in liver disease the disorganization of the liver is so great that it can no longer convert ammonia to urea, and that lactic acid, being regarded as a normal intermediate product of metabolism, combines with the ammonia and neutralizes it in the act of excretion: this is the opposite to what takes place in acid poisoning in which the ammonia neutralizes the acid, whilst under the view we are discussing lactic acid protects the body from poisoning by ammonia. In acute yellow atrophy, however, the alkalinity of the blood is reported to be reduced and, as we shall see in the following section, the administration of sodium bicarbonate is followed by a fall in the excretion of ammonia, suggesting that the ammonia is there as a base, and not because the liver cannot convert it to urea (29). If not, we should also expect the acidity of the urine to be depressed, since it is usually raised in some degree in acid poisoning. The matter, therefore, cannot be regarded as settled. It may be concluded that the evidence that lactic acid can give rise to symptoms of acid intoxication is wanting.

*Ammonia.* Ammonia is a normal constituent of the urine, rather less than a gramme, or 2 to 5 per cent. of the total nitrogen, being excreted in that form in 24 hours. This quantity is subject to considerable alteration with a variation in the diet. Thus on passing from a mixed to a protein diet the total has been observed to rise from 0·5 to 1·6 grammes with a less marked rise in the percentage of the total nitrogen excreted in this form. Ammonia is a product of protein hydrolysis, and an increase in the amount of protein used may lead to an increase in the excretion of ammonia in two ways: first, because more protein being broken down more of each of the hydrolytic products, and of ammonia with the rest, will be formed; this would not lead to any rise in the percentage of nitrogen passed out as ammonia; secondly, because some of the ammonia which would otherwise be passed out as urea will be excreted in combination with sulphuric and phosphoric acid formed from protein; if the individual was formerly upon a mixed diet containing fixed bases which performed this function, on passing to a protein diet there will be a rise in the percentage of nitrogen passed out as ammonia, as well in the absolute amount.

When a considerable quantity of base is taken in the food, as in a herbivorous animal, or when sodium bicarbonate is added to a diet, the ammonia sinks to a low level, since in the presence of abundance of base it is not needed to neutralize acid radicles. It does not, however, totally disappear from the urine. The reason for this, suggested by the writer some years ago (62), is perhaps that since ammonia is a normal metabolic product, and circulates in the blood, it must pass through the kidneys and some of it will be excreted before it can reach the liver and have an opportunity of being turned to urea.

In total starvation, and in protein starvation, such as upon a diet of starch and cream, the percentage of the total nitrogen passed out as ammonia is much raised. In such a condition the protein needs of the body are met by a disintegration of its own tissue, the minimum necessary for the performance of the required bodily functions being used. Under these circumstances the amount of urea formed is comparatively small, and instead of forming 80–90 per cent. of the total nitrogenous excretion it is only 50–60 per cent. There is, therefore, a corresponding relative increase in the proportion of the total nitrogen appearing in other forms, such as creatinin and ammonia, though the absolute amount of these bodies is but little affected. We see, then, that a rise in the percentage of the total nitrogen excreted in the form of ammonia may be simply due to a depression in the amount of urea passed out in a condition of protein starvation: such a condition may be recognized by looking at the total quantity of nitrogen passed out; should this fall below 7 or 8 grammes, a rise in the proportion of the ammonia is a normal event. The importance of appreciating this will be seen, for in the literature of acidosis it will frequently be found that acid poisoning is assumed to be present because the proportion of the total nitrogen excreted as ammonia is raised to 10 or 15 per cent., whereas on considering the total figure for nitrogen it appears that it is below 6 or 7 grammes, and, therefore, a high proportion of ammonia is to be expected quite apart from the presence of organic acids.

When mineral acids are given by the mouth and when organic acids are produced in the body the excretion of ammonia rises absolutely as well as relatively to the other nitrogenous bodies. We have seen that Walter found in a dog given dilute hydrochloric acid a rise to 1·8 grammes from a normal of 0·7 gramme. In diabetes very high figures have been obtained. In a series of observations made by Beddard, Pembrey, and myself, in one patient we observed an excretion of nearly 8 grammes of ammonia nitrogen in a day. In another case the ammonia contained 29 per cent. of the nitrogen excreted. Even 12 grammes a day have been passed out in the urine, forming 40 per cent. of the total nitrogen. The rôle of the ammonia in these cases has already been discussed: it is combined with acid radicles, with the result that the latter are excreted by the body as salts. High figures are also found in many illnesses, including gastro-enteritis, the pernicious vomiting of pregnancy, uraemia, acute yellow atrophy, and phosphorus poisoning. The significance of the ammonia in the two first-mentioned diseases will be discussed with them later.

With regard to diseases in which there is disintegration of liver tissue, it has not infrequently been assumed that a high percentage of ammonia is due to the inability of the liver to convert ammonia to urea—'hepatic inadequacy.' It may be said here that the evidence for this is incomplete. If the liver could not turn ammonia to urea we should hardly expect the administration of sodium bicarbonate to make it do so; but even in advanced cases of acute yellow atrophy and phosphorus poisoning the free use of sodium bicarbonate is followed by a diminution of the ammonia in the urine. It is, therefore,

probable that the ammonia is there as a base, having been combined with mineral or organic acids, and that when a fixed base, such as soda, becomes available, the acids take it in preference and leave the ammonia free to be transformed into urea.

Since, however, fasting alone is accompanied by an increase in the percentage of nitrogen as ammonia we should expect some of the highest percentage figures to be obtained when fasting is accompanied by acidosis. We have seen that starvation may result in acidosis, and does so with especial rapidity in the case of women and children. In a fasting hysterical woman Nebelthau found as much as 66 per cent. of the total nitrogen passed out in the form of ammonia.

Any other condition which increases the amount of organic acids produced in the body will lead to an increase in the ammonia. Thus the total exclusion of carbohydrate from the diet, protein and fat being supplied, may cause the ammonia in the urine to rise to 2 to 3 grammes a day, forming 20 to 25 per cent. of the total nitrogen. In a healthy man in good condition, however, this effect is not very marked. Beddard, Pembrey, and myself made observations upon a normal man who took a diabetic diet for three weeks. The ammonia gradually rose from 2·5 to 5 per cent. of the total nitrogen, the greatest absolute quantity passed out being just over a gramme. The addition of much fat to the diet, which, as we have seen, favours the production of organic acids, is also followed by an increase in the excretion of ammonia.

The amount of ammonia in the urine has, by some authors, been taken as a measure of the degree of acid poisoning. In a limited sense this is true. We have seen, however, that ammonia is not the only base which may be provided to neutralize acids produced in the body. The fixed bases of the blood and of the tissues, especially the bones, may be called upon, and this has been shown by Herter to take place extensively in diabetes, the amount of potassium, sodium, calcium, and magnesium in the urine being considerably in excess of the normal. It may be supposed, however, that as soon as the body begins to be depleted of these bases, ammonia plays the chief part in the neutralization of the acids. But Satta has shown that the excretion of ammonia is not necessarily parallel to that of oxybutyric acid, since a considerable fall in the excretion of oxybutyric acid was not accompanied by so rapid a fall of ammonia. Walter noticed that the fall of ammonia after a dose of mineral acid was gradual. In these cases some ammonia may continue to be passed out to save the fixed bases. Similarly, in fever, more acid bodies are excreted in the urine, the bases being raised to a less degree, with the result that the acidity of the urine is high. On the subsidence of the fever the urine becomes alkaline. We may suppose that the body, having acquired the habit of excreting a greater quantity of alkali, continues to do so until the balance of acids and bases in the body is restored. The same was seen by Beddard, Pembrey, and myself in a normal man upon a diabetic diet. The acidity of his urine was considerably increased, but on changing the diet the urine became alkaline. We should not, therefore,

expect an exact correspondence in the proportion of ammonia and of oxybutyric acid when a rapid diminution of the excretion of the latter is taking place. The quantity of ammonia in the urine may be said, then, to be an indication of the degree of acid poisoning, but not a measure of the organic acid being passed out.

The acidity of the urine, although, as stated above, generally raised in the condition of acid poisoning, is a very unsafe guide, as is apparent when we consider the power which the body possesses of neutralizing acids before their excretion. Thus Camerer found that the acidity of the urine might be unaffected when hydrochloric acid was given experimentally, the chlorine being excreted entirely in combination with ammonia. The acid sodium phosphate is not the only cause of the acidity of the urine, a part of it being due to volatile fatty acids, such as acetic, formic, and butyric acids.

A considerable degree of acidosis may also exist with very little change in the reaction of the blood. Nevertheless, in severe conditions the blood shows marked changes. The amount of ammonia in the blood is not appreciably altered by giving even large quantities of acid. The alkalinity of the blood is, however, depressed, as it is in a number of circumstances which may give rise to the production of acids in the body, such as after severe exercise in herbivorous animals, in fasting rabbits, in fevers, in puerperal eclampsia (Longridge), and in diabetes. In severe exercise and eclampsia the depression of alkalinity is probably due to an increased production of lactic acid by the muscles. In diabetes it is ascribed to oxybutyric and diacetic acids.

There is considerable difference of opinion as to the value of the methods by which the alkalinity of the blood is determined. We may assume, however, that when the observer uses the same method under constant conditions, the results are of relative, if not of absolute value. The method chiefly used in this country has been that devised by Sir Almroth Wright (73) for the estimation of the alkalinity of the serum ; it is capable of perfectly definite relative results. Jaquet found that the serum of ox blood varied less in its alkalinity than that of the whole blood.

It has been questioned whether blood of an alkalinity below normal can give rise to the symptoms of acid poisoning, since when acid is given experimentally the alkalinity may be as low as is found in disease without producing serious symptoms; but, as Bainbridge points out, the condition in the tissues is essentially different when acidosis has persisted for a long period. We have already seen that there is evidence that in chronic acid poisoning the tissues suffer severely long before the blood shows any change.

In acid poisoning, the amount of *carbon dioxide* which can be extracted from the venous blood is much less than normal. This is true of experimental acid intoxication. Thus in rabbits poisoned by mineral acid the number of volumes of carbon dioxide which could be extracted from 100 volumes of blood was found by Walter to sink from 32 to 2 or 3. In the acidosis produced by severe muscular exercise in herbivorous animals the carbon dioxide may be reduced to one-third of its normal figure. In diabetes the proportion has been as little as

10 volumes per cent. Beddard, Pembrey, and myself found figures varying from 12 volumes per cent. to 26 volumes per cent., using a method in which the blood was extracted by a syringe passed directly into a vein and not exposed to the atmosphere in its manipulation.

Jaquet concluded that the alkalinity of the blood and its content of carbon dioxide were parallel with one another, and produced experimental evidence to support this. On examining his figures, however, it will be found that the carbon dioxide only varies about 2 per cent., whilst the alkalinity varies by 10 per cent. His conclusion, therefore, is scarcely justified. It is doubtful whether the chemical condition of the blood is responsible for the low proportion of carbon dioxide, though they may both be due to a common cause. Beddard, Pembrey, and myself found that although, generally speaking, the amount of carbon dioxide obtainable from the blood varied roughly with the alkalinity of the blood, nevertheless diabetic blood was fully capable of taking up more than a normal quantity of carbon dioxide. The carbon dioxide obtainable from the blood could also be increased by placing a bandage upon the arm. We concluded, therefore, that the diminution of the amount of carbon dioxide was due to other causes. In cases showing the deep breathing characteristic of diabetic coma, the increase in the ventilation of the lungs is itself competent to pass out carbon dioxide so rapidly from the lungs that the proportion in the blood and in the alveolar air is depressed. Another possible reason is that when the tissues are poisoned by an excess of acid radicles their oxidation will be interfered with, and consequently less carbon dioxide will be formed.

Little is known of the condition of the *tissues* in acidosis. Their depletion of alkali is indicated by the constancy of the composition of the blood after large quantities of acid have been introduced into the body. Acetone is found in small quantities in healthy organs. Both oxybutyric acid and acetone have been found in the tissues in diabetes and in a case of melancholia in which these bodies were present in the urine.

## Part II

We may now turn to the more marked clinical conditions in which acidosis is suspected, and inquire how far this suspicion is justified, and in what degree acidosis, when present, may be supposed to affect the course of the disease. The acetonuria of *fevers* and of *gastro-intestinal diseases* is to be attributed to the acidosis accompanying partial or complete deprivation of food.

The one disease in which the presence of acid poisoning can be regarded as definitely proved is *diabetes mellitus*, in severe cases of which oxybutyric acid and acetone have been found in the tissues and blood, and all three acetone bodies are commonly present in the urine. The alkalinity of the blood has been found depressed, the amount of carbon dioxide in the venous blood also much lower than normal, and the ammonia in the urine increased, both absolutely and relatively to the total nitrogen. These are all signs of severe acidosis. They may exist for a long period of time during which the body becomes more and

more depleted of bases, until acid intoxication supervenes. The symptoms shown in the terminal stages of the disease, namely, rapid pulse, deep respiration, and coma passing into death, are similar to those which have been induced in experimental poisoning by acids in animals, and they appear when the amount of organic acids in the urine is greatest. If diabetes is not an acid poisoning, it must be supposed that $\beta$-oxybutyric acid, or one of its precursors, is an active poison apart from its acid properties. This is true to some extent. Desgrez and Saggio find that oxybutyric acid is definitely poisonous to guinea-pigs, when injected into a vein; more poisonous than diacetic acid or acetone, though less so than butyric acid. In health, however, $\beta$-oxybutyric acid in fair doses in man does not give rise to toxic symptoms. It might, nevertheless, do so were its oxidation interfered with. A more toxic substance, aminobutyric acid, has been put forward by Sternberg and by Grube as a precursor of $\beta$-oxybutyric acid responsible for the symptoms of diabetic coma. The evidence for this view is not, however, complete. The favourable result of the use of alkalies, to be referred to immediately, supports the view that oxybutyric acid is chiefly harmful because it is an acid. Magnus-Levy, from a calculation based upon the diminished alkalinity of the blood and tissues in diabetes, concluded that the amount of oxybutyric acid present was more than equivalent to the amount of mineral acid required to poison an animal.

It should be noted that the whole train of events concerned in the production of large quantities of organic acids in this disease may be regarded as hanging upon the failure of the diabetic to use carbohydrate. In health, the deprivation of carbohydrate may be followed by the appearance of organic acids in the urine: such deprivation can hardly, however, be total in a healthy person, because he still possesses the power of using that sugar produced in the body from protein or from fat. In the diabetic as the disease progresses this power is gradually lost. Hence, it is probable that a starving man, although he is the subject of acidosis, dies of starvation rather than of acid poisoning, for the prime condition in the production of organic acids of the acetone series is never so complete in him as in a diabetic. We have no evidence that in diabetes the accumulation of acids aggravates the gradual progress of this disability. If it were so, we should expect glycosuria to be a more prominent feature in other conditions associated with severe diaceturia; neither is there evidence that diabetic coma is due directly to the excess of sugar found in the blood and urine.

The conclusion that severe diabetes is a condition of acid intoxication derives ample confirmation from the beneficial effects of the ingestion of alkali in this disease. The administration of large doses of bicarbonate of soda to the sufferer from advanced diabetes is of the greatest advantage and may help to enable him to maintain a moderately active existence for a prolonged period; it assists the discharge of acid bodies in the urine; it is of especial value in the transition stage to a strict diet; and it may, in favourable cases, ward off a threatening coma. No one who has seen the early condition of coma recover after the exhibition of large quantities of sodium bicarbonate,

and the patient remain in a state of moderate health for many months afterwards, can doubt that his symptoms were largely due to want of base. Summarizing, it may be said that neither the injection of sugar into an animal nor the ingestion of oxybutyric acid in health produces symptoms like those of diabetic coma, whereas the administration of an excess of unoxidizable acid does so.

If it be admitted that the deprivation of carbohydrate, at first gradual but finally almost total, from which the subject of diabetes suffers is the cause, through its stimulus to the excessive metabolism of fat, of the production of large quantities of organic acids of the acetone series, and that these acids are instrumental in leading to a fatal conclusion, it must be admitted that in other conditions of partial carbohydrate deprivation accompanied by the appearance of the same acids, there is a danger of acidosis if not of acid intoxication. It is, however, extremely difficult to prove how far the acidosis present in any such condition is responsible for or contributes to a fatal termination.

The *post-anaesthetic poisoning*, first described in this country by Guthrie by the name of 'delayed chloroform poisoning', has recently attracted much attention: the discussion of its causation involves most of the points of difficulty which arise in the consideration of other states of acidosis. The subjects have usually been children who, after the administration of an anaesthetic, commonly chloroform, but, in recorded instances, also ether, ethyl chloride, and nitrous oxide, are seized with persistent vomiting, restlessness and excitement, passing into delirium, drowsiness, coma and death. These symptoms occur, in a mild degree, after an anaesthetic in a large number of cases. The only condition which is known to be common to all the cases is the administration of the anaesthetic, but several contributory causes have been suggested. Guthrie has expressed the view that since many of the subjects are rickety children, a fatty liver is an antecedent factor. Stiles and McDonald lay greater stress upon the duration of anaesthesia and upon sepsis as predisposing causes. They are confirmed in the latter, though not in the former point by Wallace and Gillespie. The urine contains acetone bodies. An increase in the ammonia nitrogen with a decrease in the urea is reported by McDonald, but such a condition, as we have seen above, is present in children deprived of food and carries no special significance: in starvation the total amount of ammonia per diem only, and not its relation to urea, is evidence of the severity of the acidosis. Leucine and tyrosine have also been found in the urine. These bodies, with other organic amido-acids and acids, are found in phosphorus poisoning, acute yellow atrophy, and other conditions associated with a disintegrative process in the liver; they are probably simply degenerative products resulting from an autolysis of the liver during life, for the same substances are found in the degenerated liver itself in experimental autolysis of that organ. After death the liver is found to be intensely fatty, as much as 17 per cent. of fat having been observed (McDonald). The heart and kidneys show a fatty appearance to the microscope, but no marked increase of fat is found in

them on chemical examination; the becoming apparent of fat previously combined is to be regarded as evidence of commencing autolysis in these organs.

Many hypotheses have been put forward to explain this train of symptoms and special prominence has been given to a supposed 'inadequacy' of the liver. A fatty liver can be experimentally produced in a very few hours by chloroform poisoning and in a less degree by ether. It is also, in common with acetonuria, a well-known result of starvation. As both the influence of chloroform and of a period of starvation are present in these cases it seems unnecessary to assume that the fatty liver found post mortem was fatty before the anaesthetic was given.

The evidence that an acid intoxication plays a large part in this condition is strong. Most of the subjects are children, in whom, as we have seen above, deprivation of food results in a condition of acidosis with surprising rapidity. Quite a considerable proportion of patients prepared for operation—25 per cent. in 127 cases observed by Wallace and Gillespie—are the subjects of acetonuria, and in these, especially among the children, vomiting was more marked after operation. The results of treatment in the interesting investigation of these workers upon post-anaesthetic vomiting, of which post-anaesthetic poisoning or delayed chloroform poisoning is an aggravated condition, support the view that acidosis is an important factor. Several writers (Waldvogel, Bainbridge, Hunter, Beddard) have suggested the administration of carbohydrate in post-anaesthetic poisoning, both as a prophylactic and as a method of treatment; sodium bicarbonate has long been used. The first measure, as the writer has emphasized (61), essays to deal with a cause of acidosis, namely, carbohydrate starvation; the second deals with the immediate condition by neutralizing any excess of acid existing in the body fluids at the time. Wallace and Gillespie's recent paper demonstrates this with considerable force. In a comparison of 72 cases treated before operation with repeated doses of sodium bicarbonate, and 100 cases treated in the same way with glucose, with 127 control cases, they found that glucose was more efficient than sodium bicarbonate in preventing the vomiting after operation. The proportion of patients showing acetone in the urine both before and after operation was also much lower in those who received glucose. On the other hand, in the treatment of post-anaesthetic vomiting when established, sodium bicarbonate has been found to be of great value. The effect of the bicarbonate on acetonuria was, as is to be expected, less definite, since alkali commonly leads to an increase of the acetone bodies, or at all events of the diacetic acid, in the urine. This result is probably to be attributed to the combination of the base with the acid enabling the latter to be excreted in greater quantity, to the advantage of the organism. Hence if acidosis be present, an increase in diaceturia after the administration of sodium bicarbonate is of good augury.

The primary condition is, of course, the administration of the anaesthetic; the preparation for an anaesthetic and its after effects involve the deprivation of food which gives rise to acidosis, especially in children. In addition to this, chloroform has a poisoning action on the tissues, especially the liver, heart, and

kidneys, and may and often does cause severe vomiting. A fatal result follows so much more rapidly in this and in many other states of acidosis when vomiting is a prominent feature, that the writer has suggested (61) that severe vomiting aggravates acidosis, and disposes to acute degeneration of the liver. On the other hand, it may be contended that the sickness is the result of acidosis and a disorganized liver when these are present in severe degree. A consideration, however, of the acidosis which occurs in cyclic vomiting, in the vomiting of pregnancy, and the increase in diaceturia observed by Rolleston and Tebbs in cases of gastric ulcer in which vomiting was a marked feature, lends some support to the view put forward.

It may be said that so far as the evidence leads us at present, the combination of the poisonous action of an anaesthetic with severe acidosis is sufficient to explain the symptoms, course, and fatal termination of post-anaesthetic poisoning. The results of the measures adopted for the prophylaxis and treatment of the milder conditions of post-anaesthetic vomiting support the view that acidosis plays a large part in the causation of the symptoms, and may pass on to acid intoxication.

The *recurrent vomiting of children* is another rare condition in which acetonuria is associated with severe vomiting and a fatty liver. $\beta$-oxybutyric acid, diacetic acid, and acetone have all been found in the urine by Edsall. Acetone has also been detected in the vomited matter. The period of acute sickness is preceded by prodromal symptoms lasting a few hours or days, consisting of malaise, loss of appetite, headache, and constipation. In the final stages air hunger has been described.

In determining whether the condition of acidosis is a primary or secondary one it is important to know whether acetone bodies have been absent from the urine before the symptoms definitely commenced; their presence in the prodromal stage in individual cases might be due to abstinence from food, and will not have the same significance as their absence. Crozer Griffith recorded absence of acetonuria in the prodromal stage, and Langmead also came to the conclusion that the acetone bodies are secondary in their appearance to the vomiting.

The cause of the attacks has been attributed to auto-intoxication from incompetence of the liver. Incompetence of the liver is a hypothetical condition of which little is known. We cannot doubt that the severe disintegration of the liver which occurs in advanced cases of post-anaesthetic poisoning, the pernicious vomiting of pregnancy, acute yellow atrophy, and phosphorus poisoning is incompatible with life. Nevertheless, the evidence that the liver which shows a moderate degree of fatty change is the cause of serious or fatal illness because it cannot detoxicate supposititious poisons derived from the intestine is incomplete at present. In Eck's fistula, in which the blood from the digestive tract is led into the vena cava without having passed through the liver, certain symptoms of poisoning occur, especially when the animal is fed upon meat, which are probably to be explained by the toxic effect of the protein fractions, in particular,

apparently, of carbamate of ammonia. In the clinical conditions we are discovering, however, the liver is seldom so disintegrated during life as not to be able to convert ammonium salts to urea; it can do this even in acute yellow atrophy, and we may be sure can do the same in the early stage of illness at which the symptoms of recurrent vomiting or of post-anaesthetic vomiting arise. Further, in both these conditions the products of proteolysis are not likely to be present in the intestine owing to the fasting or nearly fasting period which precedes an attack of recurrent vomiting, and which forms the preparation for an anaesthetic. It is hardly worth while to shelter our ignorance behind an hypothesis which can be neither proved nor disproved. We do not know what is the cause of recurrent vomiting. The evidence appears to show that the acidósis is secondary to the starvation induced, and it is probably aggravated by the vomiting. Treatment by alkali has been found to be beneficial (Batty Shaw and Tribe). The simultaneous administration of carbohydrate in the early stages is likely to be of great value. If vomiting is persistent, dextrose may be introduced per rectum, or, as suggested by Beddard in delayed chloroform poisoning, by the injection of a 6 per cent. solution into a vein. In this, as in all conditions of severe vomiting, it is essential also to remember that fluid is urgently needed.

In the *toxaemic vomiting of pregnancy* acetone bodies are found in the urine with a percentage of nitrogen in the form of ammonia which is above the normal. Figures as high as 38 and 43 per cent. have been recorded by Ewing and Wolf. A nodular necrosis of the liver has been found after death. The acidosis is evidently secondary to the starvation and vomiting (44) (71).

In *puerperal eclampsia* acidosis appears to be a less constant feature. Lactic acid is present in the blood and urine, but is not likely to be of lethal significance for the reasons already discussed. Some cases of the vomiting of pregnancy terminate in acute yellow atrophy of the liver.

*Acute yellow atrophy*, being associated with the refusal of food, is accompanied by the signs of acidosis in the urine which have been discussed in the preceding pages. The urine contains, besides the acetone bodies, other organic acids such as lactic, acetic, butyric, and succinic acids, and a large number of amino-bodies of which the most important are leucine and tyrosine. These may be regarded, as above stated, as simply the autolytic products of the degenerated liver. Or, if this is not the true explanation, another possible one is that these bodies are formed by protein hydrolysis, and that, the liver not being capable of dealing with them, they are passed out in the urine. Acute yellow atrophy is a severe toxic process, the progress of which is commonly so inevitable that no important part can be ascribed to the acidosis which accompanies it.

*Phosphorus poisoning* is another toxaemia in which the acetone bodies occur in the urine, together with other organic acids, in combination with a proportion of nitrogen as ammonia which may reach 10–18 per cent. The acidosis is secondary. The depression of the alkalinity of the blood, unlike that of simple starvation, is, in animals, only temporarily controlled by giving alkali (34).

*Uraemia* has been stated to be an acid intoxication. This view depends upon the fact, observed by v. Jaksch and several other workers, that the alkalinity of the blood is depressed. This is true of the experimental 'uraemia' which follows ligature of the ureters in animals as well as of the clinical condition. The diminished alkalinity of the blood is, no doubt, partly due to an increased production of lactic acid by the body in uraemia, for four or five times the normal amount of that acid, estimated by the zinc method, has been found in the blood. There are, however, other factors in play which have a similar effect, namely, a diminution in the number of red corpuscles and a larger proportion of water in the blood relatively to protein, each of which will lead to some depression of alkalinity. The quantity of ammonia in the urine is raised; a rise in the percentage of total nitrogen excreted as ammonia will be partly due to the partial or complete starvation which accompanies the uraemic state. An alteration of the alkalinity of the blood is not likely to be an early event, even in conditions of primary acid intoxication, for the reaction of the blood is kept constant as long as possible. But in uraemia there may be no marked depression of alkalinity until after the symptoms have become well established. This very late appearance of the alteration in the reaction, and the knowledge that it may be explained by the production of lactic acid in the last stages of a perverted metabolism, make it probable that these phenomena are only to be regarded as accompaniments of the uraemic state, not as its cause. Further, the administration of alkali is not known to delay the fatal issue.

*Scurvy* is another disease which has been attributed to acid poisoning. Ralfe suggested this view in 1877, and it has recently been supported by Sir Almroth Wright (74), who found that the alkalinity of the serum in men with scurvy was much below normal and was raised after the administration of citrate of sodium. The softening of the bones was held to confirm this, being attributed to decalcification. The experimental work of Axel Holst has thrown some doubt upon this. In a case of scurvy in an adult who for seven months had lived upon rye, wheat, bread, and water, he found the alkalinity of the blood serum was normal. He was able to produce scurvy in guinea-pigs fed upon dry cereals and water. In some of them there was a diminution in the alkalinity of the blood, but in others the reaction was normal. The administration of sodium bicarbonate did not relieve the condition, whereas it was usually prevented by fresh vegetables. Hutchison has also pointed out that foods which were believed to produce scurvy actually yielded alkaline ash, and that if the condition were one of acid poisoning we should expect to see the diabetic suffering from it. Scurvy is apparently due to one or more substances contained in fresh tissue, either vegetable or animal. Wilson has recorded how in the Antarctic Expedition the symptoms were easily dispelled by eating fresh seal's flesh. A specially interesting observation was that of Holst, that the same barley which eaten in the dry condition by guinea-pigs gave rise to scurvy, did not do so after it had begun to sprout. The content of fixed bases would be the same in each case.

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# SYNCOPAL ATTACKS, ASSOCIATED WITH PROLONGED ARREST OF THE WHOLE HEART

By E. E. LASLETT

THE patient who is the subject of this remarkable condition is a married woman aged 40. She has had no children and has enjoyed fairly good health up to four years ago, when she began to suffer from fainting attacks. These were at times of very frequent occurrence, but in the intervals she had comparative freedom from them. The patient is a bright, intelligent woman, somewhat anaemic. She suffers from breathlessness on exertion, but otherwise is able to go about her ordinary household duties except when the fainting attacks are very frequent and severe. There is a systolic murmur at the apex and pulmonary area, probably haemic in nature, but there is no enlargement of the heart. The other systems present nothing abnormal. She has been under my care for about two years, and the following remarks are based on frequent observations made during this time.

At the time when the syncopal attacks are occurring the pulse is slow and irregular, the rate often sinking to 32 and 40 per minute. This infrequency is largely due to the presence of long intermissions, which vary in length from two to five seconds as a rule, but the intermediate beats are also slow, a common frequency being 60 per minute. A tracing of the jugular pulse taken simultaneously with the radial pulse (Figs. 1-3) shows that the auricles as well as the ventricles participate in the stop, and that therefore the intermissions are due to an arrest of the whole heart. The condition is therefore quite different from what is known as heart-block. I have repeatedly listened to the heart when the pulse is irregular, and have never been able to hear any sounds during the intermissions. The fainting attacks occur only when the pulse is irregular, and so far as my observations go only when the heart has ceased to beat for three seconds or more.

With regard to the condition of the pulse and the frequency of the faintings there appears to be a cycle of events of rather variable duration. Speaking generally, the pulse remains regular (rate about 70 per minute) for the most part for a period of three or four weeks, and then intermissions begin to appear which are at first of short duration and comparatively infrequent. Frequency and duration of the stops gradually increase to a maximum, at which times intermissions of four and five seconds are quite frequent. After two or three days there is a gradual diminution in the severity of the condition until the pulse becomes normal again. The period of irregularity is usually

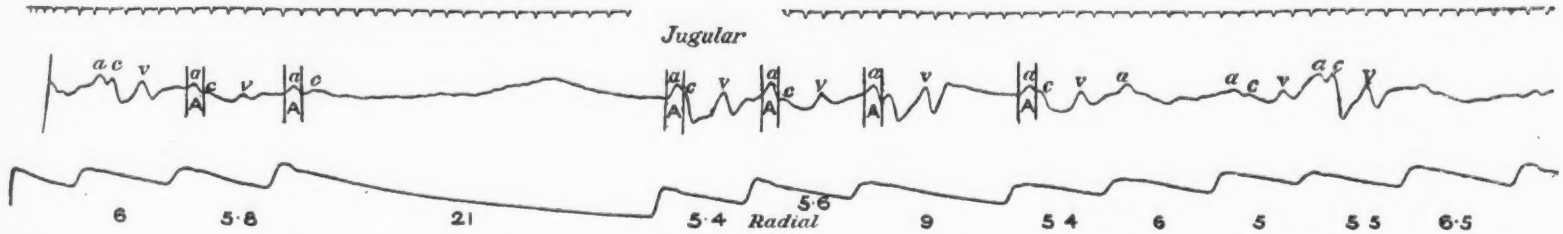


FIG. 1 shows a long pause of $\frac{21}{5}$ sec., and a short one of $\frac{9}{5}$ sec. The *a–c* interval shows no alteration after the pause, being about $\frac{1}{5}$ sec. The time-marker in this and all the other tracings records fifths of a second. Sept. 26, 1908.

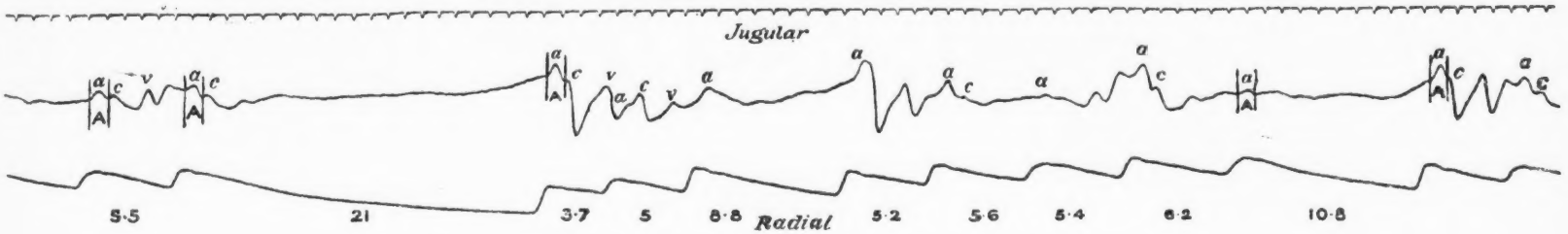


FIG. 2 is a continuation of Fig. 1. After the long pause the rate is at first frequent.

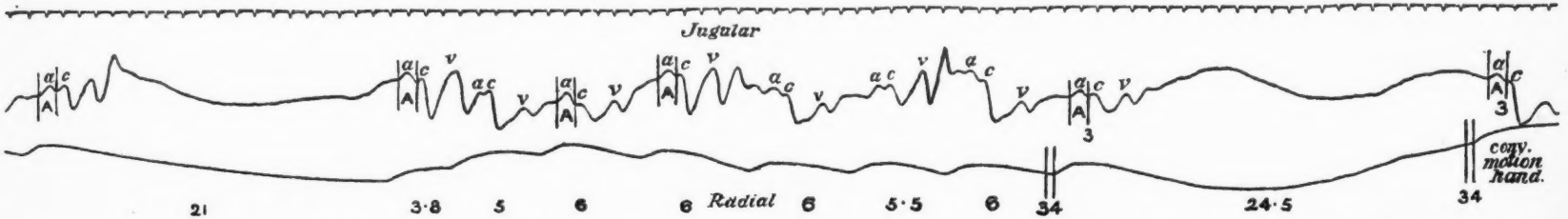


Fig. 3 was taken at the same visit as Fig. 1, but a few seconds later. A syncopal attack with slight convulsive movement of the hands occurred towards the end of the second long pause.

about a week. There are, however, considerable variations in the duration of both irregular and regular periods, and the latter is, moreover, often broken by short periods of slighter irregularity. Apart however from these temporary disturbances of the cycle, the waxing and waning of the condition are very characteristic. The frequency of the syncopal attacks varies absolutely with the frequency and length of the intermissions.

As might be expected from the variation in the length of the intermissions, the severity of the seizures varies considerably. When taking tracings of the radial pulse alone, with the patient sitting, it is frequently observed that she suddenly leans forward and puts her free hand over the heart. She feels a sudden sinking and a painful gripping over the heart. At such times the tracing always shows a stop of about three or four seconds, and if not longer than this consciousness is not lost as a rule. The gripping pain is a constant feature and causes her a good deal of distress. During the time that the pulse is continuously slow and irregular the patient is pale and has a characteristic worried and anxious look which is quite different from her usual appearance of bright cheerfulness. She is always quite aware of the intermissions, and no doubt the ever-present fear of fainting and the pain have much to do with this change of facial aspect. The more severe attacks are associated as a rule with intermissions longer than four seconds, although I have on more than one occasion counted the pulse absent for five seconds without an attack supervening. For a day or two, when the condition is at its height, the patient is in a very distressing condition. Intermissions of five seconds are quite frequent, and the patient sits pale and helpless, afraid to stand lest a severe attack should cause her to fall. On one occasion I kept her under observation for over an hour. Every few minutes the eyes closed, the facial pallor increased, she swayed to one side and momentarily lost consciousness. Only rarely is there anything approaching a convulsion, and then it is merely a slight twitching movement of the hands. Even in the worst attacks the loss of consciousness is very short, but it is frequently long enough to cause her to fall. When consciousness returns she is dazed and has a feeling of numbness and pins and needles in the extremities. Beyond this the after-effects have been slight, except on one occasion when she had loss of speech, which appears to have lasted for nearly a week. On two occasions I obtained tracings showing intermissions of six and eight seconds respectively. On the latter occasion, if not supported she would have fallen from her chair. The pulse always improves somewhat when the patient lies down, and if the intermissions are short the heart may become quite regular although slow. On this account the syncopal attacks do not commonly occur when she is in bed except at the height of the cycle.

With the exception of Figs. 5–7, all the tracings have been taken by means of Mackenzie's Ink Polygraph. Such a case as the present is well calculated to show the great utility of this beautiful instrument. Figs. 1–3 form parts of one long tracing with a break of a few seconds between 2 and 3.

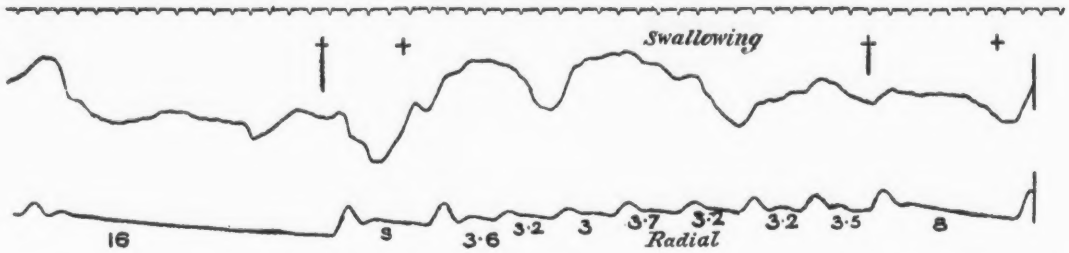


Fig. 4 shows the temporary quickening of the pulse produced by three swallowing movements made in quick succession. An intermission appeared just after the last. Sept. 29, 1908.

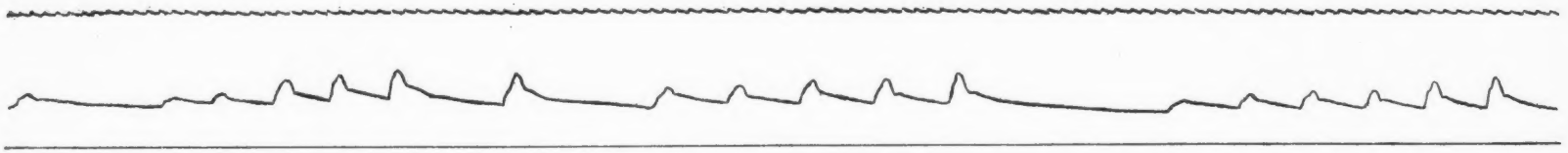

FIG. 5 shows 'staircase phenomenon' in radial pulse. The short pause measures $\frac{1}{5}^2$ sec. Anacrotism well marked in first beat after a pause. July, 1908.

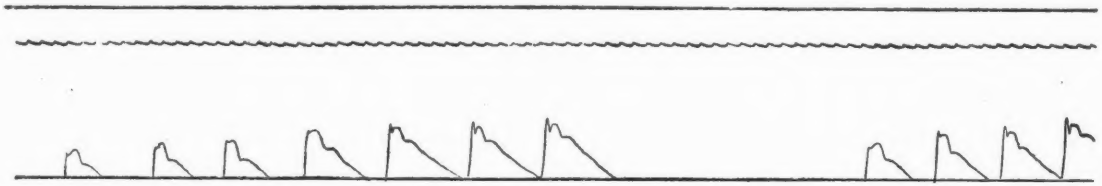

FIG. 6 shows the effect of pressure on the artery distal to the button of the sphygmograph. The first staircase came after a pause (not shown) of $\frac{1}{5}^3$ sec., the second after a pause of $\frac{1}{5}^9$ sec. Anacrotism well marked in the first two beats after a pause. Jan 6, 1909.

They serve well to show the condition of the heart when the irregularity is at its height, at which time this frequency of long intermissions is quite common. Careful examination of a large number of tracings shows that the features of all intermissions, short and long, are absolutely the same. Unlike auriculo-ventricular heart-block, in this patient the auricles as well as the ventricles cease to beat. Careful measurements of a large number of tracings show that the $a$–$c$ interval exhibits very little variation, and in particular that there is no

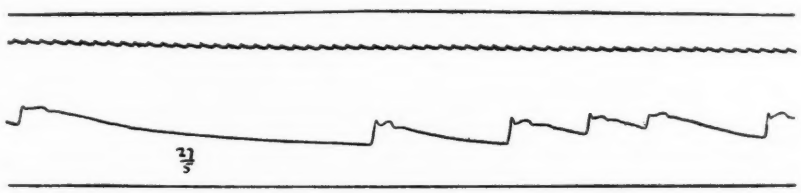

FIG. 7 shows beats of large amplitude after the long pause of $5\frac{1}{5}$ secs. The normal systolic line is not reached till the fourth beat. The first pulse-wave after the pause is anacrotic, and the rate is at first slow. Jan. 9, 1909.

alteration after a pause. This holds true in every instance, and it may therefore be concluded that there is no diminution of conductivity in the $a$–$v$ bundle. In a case of mitral stenosis Mackenzie has observed a similar condition produced by digitalin. In one instance a pause of the whole heart continued for nineteen fifths of a second. Conductivity was diminished, but it is shown that the intermissions are not due to this cause, inasmuch as the $a$–$c$ interval markedly diminishes after each long intermission. Wenckebach gives a tracing of a slow,

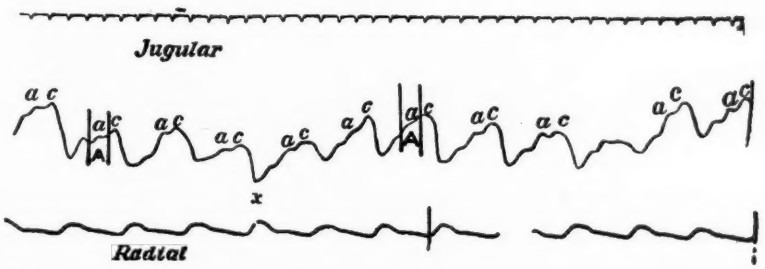


FIG. 8 shows the quickening effect of $\frac{1}{50}$ gr. atropine hypodermically. Taken fifteen minutes after the injection. Just before the administration of the atropine the pulse was slow and showed frequent intermissions of two and three seconds. Auricles and ventricles are equally accelerated. Nov. 17, 1908. Pulse 90 per minute.

irregular pulse showing long intermissions (the longest 2·5 secs.) which are probably of the same nature as those in the present case.

There are two possible explanations of the cardiac irregularity in this case which must be considered: (1) a block between the sinus and the auricle, (2) depression of the sinus rhythm by vagus inhibition. It has been shown by Wenckebach and Hewlett that blocking may occur between the sinus and auricle,

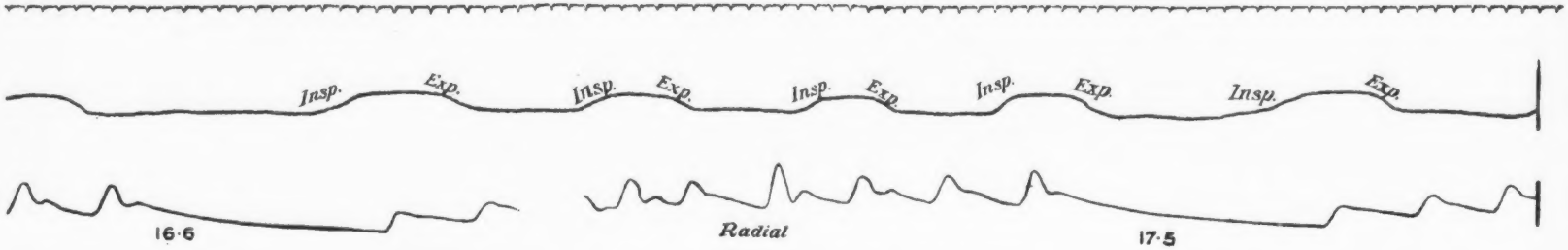


FIG. 9 shows that there is no apparent relation between the respiratory movement and the appearance of the intermissions. The 'staircase phenomenon' is more marked than is usual with the Ink Polygraph. Nov. 18, 1908.

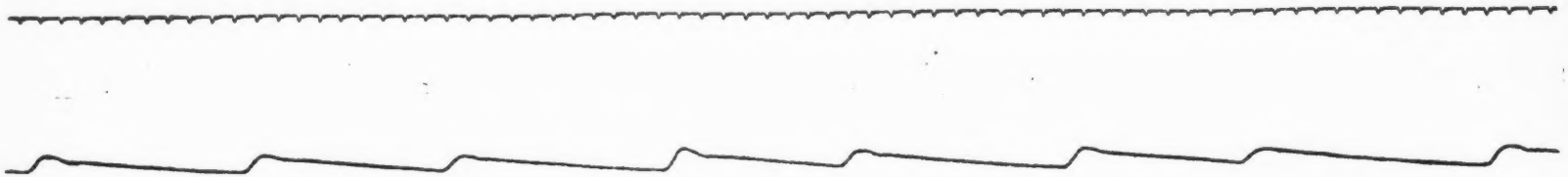

FIG. 10 shows a series of infrequent beats. The pulse remained at 30 per minute for long periods, and the long intermissions were infrequent. Jan. 9, 1909.

but in such instances the intermissions in the pulse appear with a regular rhythm such as is present in ordinary heart-block. In the present instance the intermissions appear at quite irregular intervals. Moreover, towards the end of the cycle, when the intermissions have disappeared or become very infrequent, the pulse remains slow for some days with a marked variation in rate which has no regularity in its appearances. This is well shown in the following sequence of pulse intervals, the numbers referring to fifths of a second:—6·5, 5·5, 4, 5, 6, 5·5, 7, 6, 5, 6, 7, 5, 6, 7, 5, 5, 5, 7, 6, 5·5, 7, 5. In order to be quite sure on this point, I sent a tracing to Professor Wenckebach, and he has kindly informed me that in his opinion it is a question of 'vagus inhibition or rather irregular tone of the vagus'. Mackenzie has come to the same conclusion in regard to the effect of digitalin in his case of mitral stenosis.

Two or three swallowing movements made in quick succession temporarily removed the irregularity and definitely quickened the pulse, but the intermissions began to appear immediately after the last swallowing movement (Fig. 4). On November 17, when the pulse was slow and showing frequent intermissions of two to three seconds, $\frac{1}{50}$ gr. atropine was administered hypodermically. A few minutes later the pulse began to quicken. The tracing in Fig. 8 was taken fifteen minutes after the injection, when the pulse was just over 90 per minute. The pulse eventually rose to 100 and remained regular for some hours, but next day it had again become slow and irregular. Unless the intermissions are very long, exertion and excitement will temporarily remove them, and with the same exception as already mentioned the recumbent position very quickly improves the pulse. It may therefore be concluded that the slow pulse and the intermissions are the result of increased vagus influence on the sinus rhythm—a primary chronotropic effect. A similar but slight sinus arhythmia is the origin of what Mackenzie has called the youthful type of irregularity, and this arhythmia may sometimes be respiratory in origin. In the present case the intermissions did not appear to have any relation to the respiratory movements (Fig. 9).

The action of the vagus nerve on the mammalian heart has been investigated by M$^{c}$William, Roy and Adami, Knoll, and others. In the present connexion its action on the contractility and rhythm of the ventricle is of particular interest. M$^{c}$William found that the vagus depresses the force of the ventricular systole, but this is denied by Roy and Adami. The staircase phenomenon shown so clearly in Fig. 5 is usually present, but not invariably so. There is, of course, always a considerable fall of blood pressure as a result of the intermission, but in some tracings the first beats after a pause are of large amplitude, although they do not at once rise to the previous systolic line (Fig. 7). Using Oliver's Haemodynamometer I found that a pressure of 70 mm. Hg prevented the first beat or two after a pause from coming through to the radial artery, whereas a pressure of 95 mm. was necessary to obliterate the normal pulse-wave on the same occasion. A few days later, when the pulse had become regular, the obliterating pressure had risen to 110 mm. Tracings

of the apex beat sometimes showed an indication of a staircase effect, but they were not satisfactory, owing to the difficulty of getting movements of sufficient amplitude, the apex beat being ill marked. Dr. Thomas Lewis has pointed out to me that the first beats after a pause in Figs. 5, 6 are anacrotic, a feature which v. Frey found to be present in the pulse as the heart escaped from vagus inhibition. Mackenzie's tracing also shows anacrotism. It is necessary to exercise caution in accepting the pulse-wave as an index of the strength of the ventricular beat after an intermission. There are a number of complicating conditions which must be excluded, and in particular the relative fullness of the artery before and after the pause is of importance. In Fig. 5, however, the phenomenon is particularly well marked after quite a short pause. Pressure on the artery distal to the button of the sphygmograph brings out very clearly the gradual rise of pressure and increase of amplitude (Fig. 6).

The *Treppe* phenomenon of the pulse may, therefore, with considerable probability, be taken as evidence of diminished extent of the ventricular systole, whether this diminution be due to lessened contractility or, as Muskens holds in the case of the frog's ventricle, to diminished conductivity within the heart-wall. The staircase phenomenon is shown beautifully in some of the tracings of Webster's remarkable case. Here, according to Wenckebach, there was at times heart-block, at other times a pure negative chronotropic effect.

With regard to the rhythm of the ventricular beat, McWilliam believes that the vagus can depress this as well as the contractility. He found that the ventricle as a rule followed the auricle in the period of inhibitory pause, and, considering the high rhythmicity of the ventricle, he concluded that its rate was depressed as well as that of the auricle. On the other hand, Erlanger and others from observations on heart-block in man and the dog have concluded that the vagus has only slight, if any, action on the ventricular rhythm. It is perhaps a noteworthy point, that in the present case, in all the many intermissions, both long and short, of which tracings were obtained, the ventricles did not once show a beat independently of the auricles. As a general rule, a long intermission appears suddenly, but occasionally there is a preliminary slowing for one or at most two beats. On the other hand, I have not been able to satisfy myself that there is ever a diminution of pulse amplitude immediately before the appearance of a stop, although in one or two tracings obtained there is a slight indication of this. After the pause, the frequency most commonly increases gradually, but there are many exceptions to this rule. Occasionally there is a long series of infrequent beats (Fig. 10), and when this occurs the pulse always quickens considerably before a long intermission appears. As already mentioned, the normal pulse-beat is about 70–72 per minute, but excitement or exertion will readily raise it to 100 or higher, and, except when the pulse is very slow, the patient is always liable to attacks of palpitation from emotional causes.

In a recent paper Russell has suggested that epilepsy is due to sudden temporary failure of the cerebral circulation. The cerebral attacks in the

present case have often considerable resemblance to petit mal, and their obvious association with and dependence upon the stoppage of the heart are of interest in relation to this theory. As to the ultimate origin of the increased vagal action, one can express no decided opinion. At present the patient is a bright, intelligent woman, but if, as she thinks, the condition is becoming worse, the effect upon the brain, one would suppose, must ultimately be serious. Although at other times she enjoys fairly good health, at the height of the inhibitory period her condition is distressing in the extreme.

It is a pleasure to express my great indebtedness to Dr. James Mackenzie. Had it not been for his continued kindly encouragement and advice, this record would have been much more incomplete. To Professor M°William and Dr. Thomas Lewis I am also greatly indebted for help in the interpretation of the tracings.

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# IRREGULAR ACTION OF THE HEART IN MITRAL STENOSIS: THE INCEPTION OF VENTRICULAR RHYTHM, ETC.

By THOMAS LEWIS

The recent development of the exact study of cardiac records has led to a rapidly increasing accumulation of facts of considerable importance in relation to many problems of physiological and clinical interest. But in some directions, though observations of a highly suggestive nature have been made, our knowledge is still very deficient. The statement applies with peculiar force in two directions. Thus, it is only of recent years that it has been possible to recognize in many specific instances that the vagus has been responsible for certain morbid cardiac phenomena, while at the same time the cause of such 'vagal attacks' has not been determined, and the question whether the vagus has any direct influence upon the human ventricle still remains unsolved. Again, while it is now generally held that the sinus inaugurates the whole cardiac cycle, and that at the same time all parts of the contractile heart-wall are capable of exercising a rhythmic function, yet the factors determining the development of such rhythmic properties, and influencing the rate of production of rhythmic impulses, more particularly at the lower heart levels, are still obscure.

The facts recorded in this communication relate in the main to these questions. It will be advantageous if the history of a case of mitral stenosis is first detailed, and if the accompanying tracings are then briefly described. Finally, the conclusions which the observations appear to warrant, and their bearing upon recent investigation, may be noted.

The patient, a young adult of 19 years, was first seen in Dr. Rose Bradford's wards on Dec. 19, 1908, and the writer is indebted to Dr. Bradford for his kindness in allowing the examination of the patient and in permitting the publication of these notes.

*History.* The patient suffered from acute rheumatism when 8 years of age, but had otherwise been exempt from illness until 1907. He was then admitted to University College Hospital with a two months' history of shortness of breath, and pain over the region of the sternum, upon exertion. He was found to have a prominent praecordium, and an area of cardiac pulsation reaching from the second to the fifth left spaces. The limits of cardiac dullness were one inch external to the nipple on the left, half an inch to the right of the sternum and above to the third rib. There was a diastolic and presystolic thrill at the apex, a systolic and rough presystolic murmur at the apex, and an early diastolic murmur in the fourth space near the sternum. The second sound was reduplicated. He was admitted a second time in October, 1908, with similar symptoms.

[Q. J. M., July, 1909.]

By occupation a barman, he stated that he had never smoked or drunk excessively. He had never had dropsy. The pulsation of the chest-wall extended over the fourth to the sixth spaces, and reached a point two inches external to the nipple line; it was also noted to the right of the sternum and in the epigastrium. The impulse, which was maximum in the fifth space near the sternum, was diffuse and strong. It was preceded by a well-marked thrill, and was succeeded by a notable diastolic shock. Percussion showed the limits of lateral dullness 1 inch to right of sternum and 1½ inches external to nipple line. Systolic and presystolic murmurs were noted.

Dec. 19, 1908. When first seen by the writer, the following alterations in the physical signs were apparent. The presystolic murmur and thrill were absent and were replaced by an early diastolic murmur and thrill, noted over a considerable area of the lower praecordium. The murmur was rough and broken. A purer murmur of softer quality was audible in the third and fourth left space. The second pulmonary sound was increased, the second aortic normal. There were no definite signs of aortic regurgitation. Tracings from the neck showed the auricular type of venous curve. Those from a well-marked apex beat in the fifth space showed complete absence of an auricular wave. The *a–c* interval was a little long; the patient had been on digitalis (5j of the infusion) for a week. Marked irregularities of the radial pulse were noted on the next and succeeding days.

The irregularity noted on Dec. 20, 1908, is exampled in Figs. 1, 3, 4, 5. In the radial tracing it is seen to consist of a gradual increase in the length of the pulse beats, and a subsequent decrease of the same. The central beats of such phases are of considerable length, and of these there may be one, two, or three, varying from $\frac{6{\cdot}0}{5}$ to $\frac{7{\cdot}2}{5}$ sec. The occurrence of these phases was frequent, as may be seen by reference to the accompanying table, which represents an analysis of the phases of a single tracing. The lengths of the pulse beats are stated in fifths of a second, and the phases are so placed that the longest beats lie in corresponding columns. The arrows are inserted where one phase runs into the next. The table shows the striking uniformity of the phases, the gradual onset and offset of each.

| No. of Phase. | Lengths of pulse waves in fifths of a second. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 3·7 | 3·8 | 4·0 | 6·5 | 6·5 | 4·9 | → | | |
| 2 | | | | | 6·5 | 6·0 | 4·2 | → | | |
| 3 | | | 4·1 | 4·2 | 6·8 | 6·6 | 5·2 | 4·4 | 4·5 | |
| 4 | | | 4·3 | 4·7 | 6·7 | 6·1 | drum stopped | | | |
| 5 | 4·0 | 4·2 | 4·6 | 4·7 | 7·0 | 6·0 | 4·2 | 3·8 | 4·0 | → |
| 6 | | | 4·0 | 4·0 | 6·8 | 6·0 | 4·8 | 4·4 | → | |
| 7 | | | 4·0 | 4·1 | 6·8 | 6·0 | 4·6 | 4·1 | 4·0 | |
| 8 | 4·0 | 4·1 | 4·2 | 4·2 | 6·3 | 6·0 | 4·3 | 4·1 | → | |
| 9 | 4·0 | 4·0 | 4·0 | 4·0 | 6·3 | 6·3 | 4·2 | 4·2 | 4·2 | → |
| 10 | | | 4·0 | 4·2 | 6·6 | 6·0 | 4·5 | 4·0 | 4·0 | |
| 11 | 3·8 | 3·5 | 3·5 | 4·0 | 6·0 | 6·6 | 5·2 | 4·6 | 4·5 | |
| 12 | 3·9 | 3·9 | 3·9 | 4·0 | 6·3 | 5·8 | 4·4 | 4·0 | 4·0 | |
| 13 | 4·2 | 4·0 | 4·0 | 4·2 | 6·7 | 6·0 | 4·2 | 4·0 | | |
| 14 | 3·8 | 3·8 | 3·8 | 4·5 | 6·5 | 5·8 | 4·4 | 4·0 | 3·9 | |
| 15 | 3·9 | 4·0 | 4·5 | 4·7 | 6·7 | 6·7 | 4·2 | → | | |
| 16 | | | | 4·0 | 6·6 | 6·3 | 5·0 | 4·5 | 4·5 | |
| 17 | 4·2 | 4·3 | 4·3 | 4·4 | 6·5 | 6·1 | 4·1 | 4·0 | 3·9 | |
| 18 | 4·0 | 4·0 | 4·8 | 4·8 | 6·4 | 6·2 | 4·2 | 3·9 | 4·0 | |

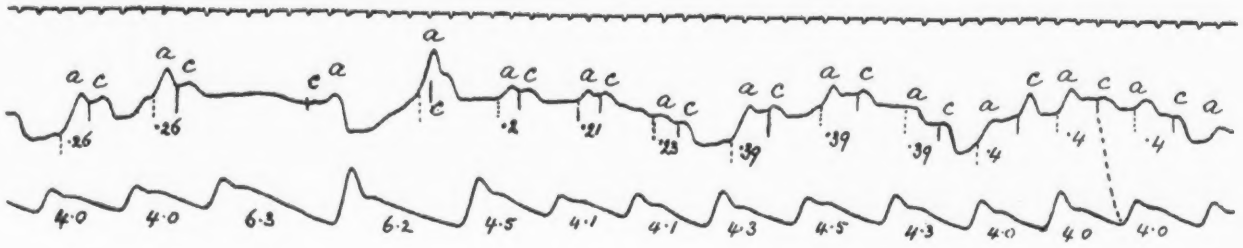


FIG. 1.

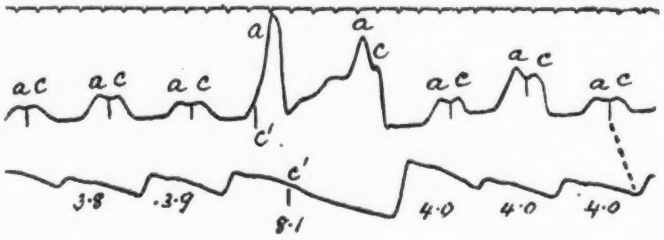


FIG. 2.

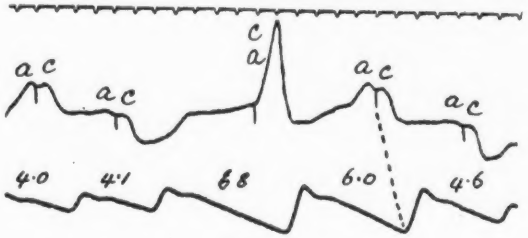


FIG. 3.

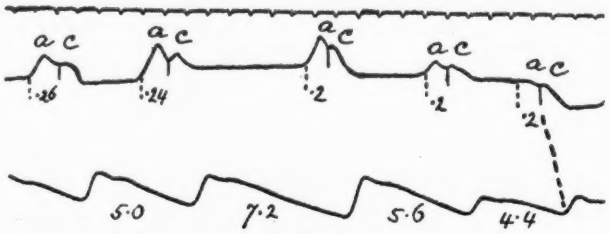


FIG. 4.

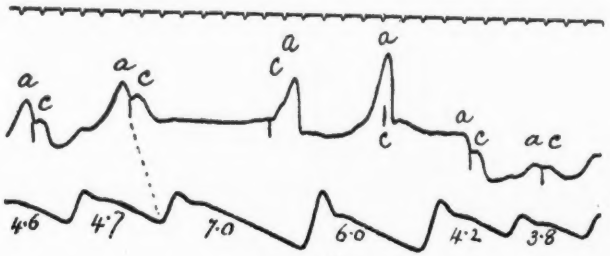


FIG. 5.

On referring to the figures it will be found that the *a–c* interval is usually of abnormal length before the occurrence of a phase, and this was also a notable feature in longer periods of the tracing in which no such phases occurred. It will also be observed that there is a tendency towards a return to the normal interval, namely 0·2 sec., subsequent to a phase (shown well in Figs. 1, 4, and 5). As a rule such a shortened interval quickly gave place to longer ones, and at times the lengthening became very marked, as shown in Fig. 1. Occasionally the long intervals shown in the last part of this curve (Fig. 1) continued for some time (a portion of such a curve is given in Fig. 6, where the *a–c* interval measures 0·5 sec.). As a rule, such an increase of the *a–c* interval was accompanied by an increase of pulse rate, but not consistently. Thus, as shown in Fig. 1, with the sudden increase from 0·23 to 0·39 sec. there is a temporary decrease of the pulse rate.

Such, briefly, were the actual changes manifested previous and subsequent to the phases. The phases themselves, as they occurred spontaneously, bore no fixed relationship to respiration, neither could they be developed by inducing the patient to swallow repeatedly. They could be brought out, during long

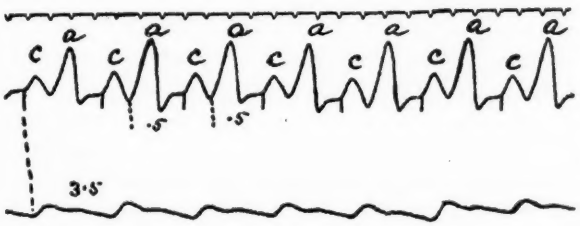


FIG. 6.

intervals over which they otherwise failed to appear, by forced breathing. They could also be produced by deep pressure in the carotid region on the left side of the root of the neck.

The analysis of the phase itself is of chief interest. It will be seen at once that there is slowing of both auricle and ventricle, but that the slowing in the rhythm of one and the other does not necessarily run parallel. A few of the more striking examples are given in Figs. 1, 3, 4, and 5. In Fig. 4 the *a* and *c* waves are in their normal positions in relation to one another, and the phase is due to a slowing of the whole heart, which receives complete explanation if we assume a primary slowing of the pace-making sinus. In the case of Fig. 3 (phase 7 in table) this explanation requires amplification, for, following the long pause of $\frac{6{\cdot}8}{5}$ sec., a large wave occurs at the onset of ventricular systole. That this wave is a compound of the *a* and *c* waves will be more evident when all the curves are more closely examined; and the interpretation is fully substantiated by the curve shown in Fig. 2. This tracing was taken on the next day, and shows a single extra-systole of ventricular origin. The *a* and *c* waves have fallen together, or

more correctly the auricle has contracted while the ventricle was in systole, and a large wave reaching the time tracing has resulted. Following the second long pause of Fig. 3 the *a* and *c* waves resume their normal relationship. In Fig. 1, after the first pause, *c* actually precedes *a*; after the second pause *a* precedes *c* by a shortened interval. In Fig. 5 (phase 5 in table) very similar events are shown.

Adopting the interpretation advanced in conjunction with MacNalty in a recent communication (an interpretation also put forward in an almost simultaneous publication by Wenckebach), it is held that where the *c* wave occurs at an earlier time interval than the *a* wave the ventricular systole which it represents is the result of stimulus formation at a level in the heart lower than the sinus. In the case then considered it was supposed that stimulus matter was built up both in sinus and ventricle, and that the ventricle responded to auricular contraction or to its own stimulus according to the time relationships of contraction of the various cardiac chambers. For the time being the question may be left at this stage, and further explanation and discussion will be offered when the remaining curves have been examined. (It may be stated that in his recent communication Wenckebach has published some curves from a case of chronic interstitial nephritis, which closely resemble those which have just been described.)

It will be remembered that when the patient was first seen he was under the influence of digitalis. On the day upon which the first tracings were taken the dose of the infusion was increased from 1 to 1½ fluid drachms. On the next day similar phase variation in the pulse was noted, and on that and subsequent days the dropping out of ventricular beats was observed. An instance of this nature is given in Fig. 7. This curve is one of the more complex obtained and requires careful consideration. It will be seen that the radial pulse is not quite regular, the beats vary from $\frac{3{\cdot}1}{5}$ to $\frac{3{\cdot}8}{5}$ sec., and that at one point a pause of $\frac{4{\cdot}9}{5}$ sec. occurs. It is here that the ventricular beat is dropped, for there is no response to $a^9$. The curve was taken during a suspension of respiration and shows several points of interest. The comparatively short length of the pause during which the dropping out of a ventricular beat takes place is due to the relatively short *a*–*c* interval succeeding it, and also in part to another factor. Up to the point where the beat is dropped there is a gradual increase of auricular rate. Thus, while, so far as measurements allow, the *a*–*c* intervals show no regular increase in length, the *c*–*a* intervals diminish. As a result *a* mounts further and further up on *c*, and from the commencement of the tracing up to the dropped beat the venous curve as a whole shows an increased excursion. Subsequent to the dropping of the beat the *a*–*c* interval falls to 0·3 sec. and the amplitude of the venous curve is again reduced. Towards the end of the tracing it is once more increased, but on this occasion its increase is brought about in a different way.

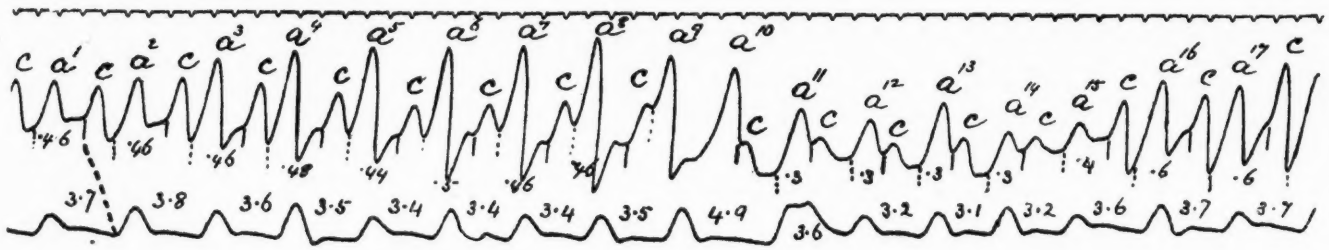


FIG. 7.

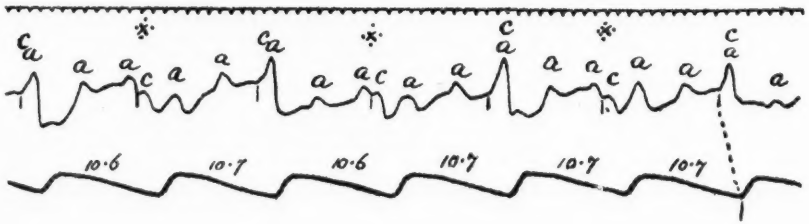


FIG. 8.

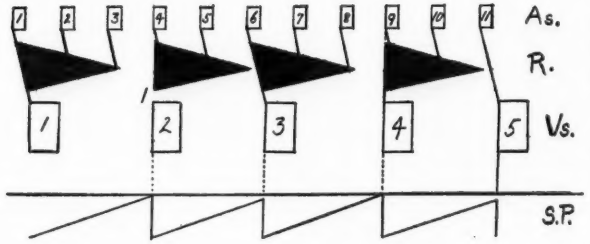


FIG. 9.

Here the pulse is slowing. It is to be attributed to an absolute increase of the *a–c* interval, and consequent decrease of the *c–a* interval. (Wenckebach has recently published this explanation of the increased prominence of the *a* wave; it was previously recognized by several of those engaged in venous pulse work. A curve illustrating it very beautifully was published by Mackenzie in the *British Medical Journal* for March, 1905, Fig. 3, p. 588.) As in Fig. 1, the increase of the *a–c* interval is again accompanied by pulse-slowing and consequently cannot be attributed to fatigue of the bundle.

The last tracing of the present series (Fig. 8) was taken from the patient, a subject of permanent heart-block, who formed the basis of the communication by MacNalty and the writer which has been referred to. It shows what appears at first sight to be a condition of complete heart-block, for at intervals the auricular and ventricular systoles have coincided. The interpretation of the curve rests largely upon previous observations, for it was shown that in this patient sinus and ventricular stimulus production were both active, and that occasionally the ventricle responded to auricle and occasionally contracted as a result of its own inherent stimulus production. The present tracing is another example of the same phenomenon, and one in which there is a curious alternation of the responses to the two sources. The close approximation of the lengths of the radial beats in itself suggests a pure ventricular rhythm, and it might be held that the occurrence of *ac* waves in their usual sequence at the points marked * is purely coincidental. Such an interpretation would perhaps be plausible so far as this short strip of curve is concerned, for the error of measurement is relatively large. But it becomes quite untenable in view of the fact that the alternation, as figured, was observed for long periods of time. The possible error consequently becomes extremely minute and the probability of coincidence diminishes to a corresponding extent. The curve given is one taken at a slow speed, that more beats may be shown. In faster curves a slight alternating difference in the lengths of the radial beats was a notable feature. Those pulse beats which accompanied superimposed *a* and *c* waves tended to be slightly shorter than those accompanying *ac* waves. The factors involved in the production of this heart irregularity may be best appreciated by reference to Fig. 9. The diagram represents a series of regularly-occurring auricular beats (As), each of which sends its impulse (represented by an oblique line) towards the ventricle. The beats marked 1, 6, and 11 respectively occasion ventricular responses (Vs). All other auricular impulses are held up by the refractory periods (represented by the black triangles). In the lowest line of the diagram, stimulus production in the ventricle is illustrated, and the ventricular responses occasioned by it are drawn as occurring when the zigzag reaches the horizontal line. The rate of stimulus production is constant throughout, and the accumulating stimulus material is represented as destroyed at each ventricular contraction (the full evidence for which is given in the paper already referred to). A careful study of the diagram will show the possibility of the events of Fig. 8 occurring as they are here interpreted, namely, as the result of alternate

response of the ventricle to stimuli derived from two sources. It will be seen that the phenomenon depends upon the relationship of auricular rate to the length of the refractory periods, and *par excellence* to the rate of ventricular stimulus production. In the diagram the differences in the distances between the ventricular beats have been deliberately exaggerated for explanatory purposes. Under special circumstances their spacing might well be uniform within the limits of the error of measurement. It is also to be noted that the refractory periods have been inserted as following spontaneous ventricular beats, an assumption which is justified by the failure of response to the fifth and tenth auricular beats.[1]

*Discussion of the Foregoing Observations.*

(*a*) *The presence of the auricular form of venous pulse subsequent to the disappearance of a presystolic murmur, and its significance.* The notes of the case given in the early pages of this paper place beyond doubt, first, the presence of stenosis of the mitral orifice, and secondly, the disappearance of a previously observed presystolic murmur. The presystolic murmur is unquestionably due, in part at least, to the contraction of the left auricle.[2] And it may also be said that it is established more particularly as an outcome of the work of Mackenzie, that the disappearance of such a murmur is due to deficiency of the auricular contraction at the usual period in the cardiac cycle. In this patient the view is substantiated by the absence of an auricular wave from the prominent apex beat (the publication of this curve is deemed unnecessary). Now while paralysis of the left auricle in mitral stenosis cannot be regarded as a new observation, yet the absence of its contraction at the usual instant in the cardiac cycle, in the presence of the auricular type of venous pulse, has never, so far as the writer is aware, been placed on record. The facts allow of but one conclusion, namely, that while the right auricle was active and contracting at the usual instant in the cardiac cycle the left auricle was paralysed. Contraction of the right auricle at the usual instant in the cycle, and contraction of the left auricle during ventricular systole, require no discussion. The significance of the conclusion is in respect of the ultimate elucidation of the common condition termed by Mackenzie 'nodal rhythm'. It is now held by this author that the ventricular form of venous pulse results from the simultaneous contraction of auricle and ventricle, and that it is produced by an irritative lesion of the auriculo-ventricular node. The evidence for the view is strong, but perhaps as

[1] The interest of this suggestion lies in the fact that supposing one admits that it is the bundle which is refractory, one must also suppose that the spontaneous ventricular contraction involves the bundle, that is to say travels back. The same assumption has to be made in certain instances of extra-systole in partial heart-block. The whole question is intimately related to the possibility of the occurrence of retrograde extra-systole in man.

[2] Any doubts as to the actual time of onset of this characteristic murmur have finally been laid at rest by the graphic records of Weiss and Joachim.

yet inconclusive. It may be said, however, that in certain instances the hypothesis is supported by more facts than any other. One of the chief arguments adduced in favour of it is Mackenzie's observation that in mitral stenosis its appearance is simultaneous with the loss of the presystolic murmur (an observation which has been confirmed by Hewlett and others). The ventricular form of venous pulse has also been explained as a result of auricular paralysis. Such a view cannot meet with acceptance so long as Mackenzie's observation stands, for in the first instance paralysis as a result of back pressure must necessarily affect the left auricle. While the present observations show the possibility of primary paralysis of the left auricle,[3] they cannot be said to invalidate Mackenzie's hypothesis; the train of events may vary from case to case; they are recorded and discussed mainly that attention may be drawn to the possibility of such primary paralysis, and to the importance of ascertaining the frequency of its occurrence.

(*b*) *The prolongation of the a–c interval in mitral stenosis and the influence of digitalis upon the heart in this condition.* The delayed contraction of the ventricle in certain cases of mitral stenosis was first fully described by Mackenzie, and has since been confirmed by other observers (Herringham and Hay).[4] It has also been shown that this partial degree of heart-block is increased by digitalis. From this aspect the present observations are incomplete in that neither before nor after the administration of digitalis was there any opportunity of obtaining records.[5] It is consequently sufficient to state that in so far as they go they are in complete accord with previous statements.

(*c*) *The further interpretation of phasic variations in the length of the radial pulse beats, and remarks on the inception of new cardiac rhythms.* We have seen that there is reason to believe, both in the case of the patient with mitral stenosis and in the case of permanent heart-block (Fig. 8), that temporary dissociation of auricular and ventricular contraction occurred. In both cases the ventricle responded occasionally or often to auricular impulses. In both the ventricle exhibited contractions which could not rationally be attributed to this source. In the case of heart-block there is little reason to doubt that the site of stimulus production lay at a lower level than the site

[3] The right auricle continuing to functionate in a normal manner.

[4] The prolongation of the interval between auricular and ventricular systole in mitral stenosis was recognized by Mahomed (*Med. Times and Gazette*, 1872, i. 570) and by Galabin (*Guy's Hosp. Rep.*, 1875, 282). The latter gives very beautiful cardiograms demonstrating this prolongation, and remembering that the author was speaking of the mechanism of production of the auriculo-systolic murmur, attention should be drawn to the fact that he noted the absence of this murmur in a case of mitral stenosis where no auricular wave could be found in the cardiogram. Galabin was evidently aware that the disappearance of the murmur in mitral stenosis was to be ascribed to failure of the normal auricular contraction. Mahomed and Galabin also gave tracings showing dropped beats, and the latter recognized the significance of his observation. His paper forestalled that of Chauveau, which is usually quoted, by ten years.

[5] The *a–c* interval in this patient has since been observed to exceed 0·2 sec. under ordinary conditions.

of the block, and as we have reason to believe that such block occurred in the auriculo-ventricular bundle (the evidence for which is dealt with at length in the *British Medical Journal*, 1908, ii. 1798), it is rational to conclude that it must be placed in some part of the ventricular wall.[6] In the instance of mitral stenosis the problem is not quite so easy to deal with. It is to be observed that the distances from the added ventricular beats to the preceding ventricular beats vary considerably, and it might be held that the added beats arose, not from one, but from several foci. For, as shown by MacNalty and the writer, there is a marked tendency for spontaneous ventricular beats to be preceded by pauses of constant length. Given, alone, such an instance as that figured (Fig. 3), the simultaneous contraction of auricle and ventricle might be regarded as nodal in origin. The impossibility of correlating the length of the preceding pause and the level at which the particular impulse may be supposed to have arisen favours the rejection of this view. Thus in Fig. 4, the longest pause, $\frac{7.2}{5}$ sec., is succeeded by *ac* waves; while in Fig. 1 an isolated *c* wave is preceded by a pause of $\frac{6.3}{5}$ sec. only. Therefore the view adopted is that the added ventricular beats were of ventricular origin and that their varied relationship to auricular contraction was coincidental. An additional factor for the variation in length of the spontaneous ventricular beats must consequently be sought and may be mentioned later.

The demonstration of the activity of the ventricular or lower level rhythm in these instances is of interest. We are as yet unaware to what extent the rhythmic production of stimuli in the ventricle is active or dormant in the normal state. Erlanger and Hirschfelder found that, when the *a-v* bundle was crushed, long ventricular silences occurred, and the length of such pauses was shown by them to be related to the rate of crushing or clamping. It is possible,

[6] Hering (*Pflüger's Archiv*, 1909, cxxvi. 225) has recently found that when the ventricle is cut off from auricular stimuli the sequence of contraction in the several parts of its walls is identical with the sequence of contraction in the ventricular beat of auricular origin. As he states, the observation is evidence that in complete heart-block the stimulus production in the ventricle occurs in the bundle itself below the level of the block, and the view is supported by the fact that the ventricular electro-cardiogram is identical with the normal curve. A ventricular extra-systole shows a highly atypical electro-cardiogram, and Kraus and Nicolai (*Deutsche med. Wochenschr.*, 1908, 1) appear to have demonstrated that the curve in extra-systole varies according to whether such a beat arises in right or left ventricle. The evidence which the same authors bring forward for the view that the ventricle, in which the extra-systole is produced, contracts more strongly, that is to say the evidence for hemi-systole, partial or complete, is not conclusive. In a case reported in *The Lancet*, 1909, i. 382, an instance of multiple and successive extra-systoles is given. The extra-systoles occurred so frequently in comparison to normal beats, that any appreciable grade of hemi-systole would of necessity have brought the circulation to a standstill. As a matter of fact, in the patient instanced, the disturbance of cardiac rhythm, though long continued, produced comparatively little interference with the circulation. For the time being the type of ventricular electro-cardiogram should be regarded as purely an indication of the direction of contraction in the ventricle, and as such it allows the deduction, within certain limits, of the point at which the new stimulus arises.

as they suggest, that the *gradual* cutting-off of auricular impulses leads to an awakening of ventricular rhythmicity. Be it as it may, the presence of rhythm activity in the ventricle must necessarily be of prime importance to the well-being of the subject of incomplete heart-block. The collected figures show that isolated pauses of 3 sec. between ventricular beats are usually associated with the onset of unconsciousness, and that longer pauses may terminate in epilepsy. In partial heart-block with pauses of $1\frac{1}{2}$ to $2\frac{1}{2}$ sec., any increase in the block may result in a disturbing or disastrous diminution of the pulse rate; and it may well be that the situation is often saved by the awakening of inherent ventricular rhythm. Such appears to have been the case in the patient from whom the curve shown in Fig. 8 was taken. Despite the usual frequence of fits in incomplete heart-block, this man has experienced no nervous disturbances of consequence in the seven months during which he has been under observation.[7]

(*d*) *The causation of the phasic variations in the case of mitral stenosis.* The origin of the phasic variations of pulse length, in the case described, is closely associated with the causation of the prolonged *a–c* interval and the action of digitalis in increasing heart-block. A full review of the evidence bearing upon the subject would be out of place. That the phases were due to vagal inhibition is strongly suggested by their temporary and periodic nature, and by their close resemblance (more particularly Fig. 4) to curves produced in animals by weak vagal stimulation, and to the respiratory variations seen in the human subject with forced breathing and in dogs even during quiet respiration. Such respiratory variations are of undoubted vagal origin. A few of the more prominent observations bearing upon the subject may be noted. Pharmacological experiment has demonstrated that digitalis influences the heart-beat *via* the vagus (Cushny). Low grades of heart-block in animals are increased both by vagal stimulation (Gaskell), and by digitalis (Tabora). In man, heart-block may be increased by pressure on the vagus (Rihl), and by swallowing (Mackenzie). Digitalis may produce temporary standstill of the whole heart, and the succeeding beats may manifest the staircase phenomenon (Mackenzie). Lastly, when there is a tendency to a cyclic disturbance of the heart's action, as in the case of mitral stenosis, the frequency of the attacks can be increased, or in other words attacks can be initiated, by pressure on the vagus (Wenckebach and these observations), and by deep breathing. That the vagal tone was increased during the phases is therefore in the highest degree probable. The variation in the pauses preceding the spontaneous ventricular beats suggests (as Wenckebach states) that in man the inhibitory influence is exerted directly upon the ventricular musculature, but though suggestive, the variation in itself cannot be regarded in the present state of our knowledge as more than contributory evidence towards the solution of an intricate problem.

[7] Since these pages were written the patient has had two fits, each of five minutes' duration.

## EXPLANATION OF FIGURES

In all tracings, Figs. 1–8, the upper line represents time in fifths of a second; the middle line is the jugular, and the lowest line the radial curve. A dotted line is in each figure drawn from a radial beat to the corresponding *c* wave. In every instance such lines were estimated by careful measurement from a carotid and radial curve. The *a–c* intervals are marked in seconds, and the lengths of radial pulse beats in fifths of a second.

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# THE PATHOLOGY OF PAROXYSMAL HAEMOGLOBINURIA: A CRITICAL REVIEW [1]

By G. H. K. MACALISTER.

Experimental evidence has shown that the injection of haemoglobin into the circulating blood, or the setting free of haemoglobin by the solution of red corpuscles, leads to a great increase of bilirubin. The iron-containing part of the haematin is split off and retained, probably in the liver. It has been stated by Hayem that the serum which separates from blood always contains free haemoglobin—that there exists, in other words, a physiological haemoglobinaemia. Schäfer was, however, unable to prove this experimentally. Whether it be true or not, these experiments show that haemoglobinaemia, however produced, results first in an increase of bilirubin and so in polycholia.

The power of the liver to cope with a pathological or experimental haemoglobinaemia is great. But when the quantity of free haemoglobin in the serum passes a certain point, use is made of a more direct means of exit, and the result is haemoglobinuria. Ponfick and Stadelmann, independently, have shown that this does not occur until the amount of free haemoglobin reaches one-sixtieth of the total haemoglobin content of the body. Camus more recently has shown that a destruction of red cells equivalent to one-fifty-seventh of the total haemoglobin of the body may take place without any appearance of the pigment in the urine. The spleen and marrow, he states, come to the help of the liver and the haemoglobin is there stored in the form of haemosiderin. If the products be thus stored, regeneration of the blood is more rapid than would be the case if the pigment were entirely lost.

It is obvious therefore that while, in the light of our present knowledge, haemoglobinuria is impossible without a preceding haemoglobinaemia, the degree of haemoglobinaemia required to produce haemoglobinuria must always be very large. In any investigation of the pathology of paroxysmal haemoglobinuria, it is necessary to consider first the nature of haemolysis in general and the various factors which may cause it.

1. In the first place, haemolysis may be due to purely physical causes. Trituration of red corpuscles with sand will cause their disintegration. The addition of distilled water or the alternate freezing and thawing of blood will also cause haemolysis.

[1] A Thesis presented for the degree of M.D. in the University of Cambridge.

Q. J. M., July, 1909.]

2. Some chemical substances such as alcohol, urea, ammonium chloride, and glycerine penetrate the red cells and disorganize them. Injection of 10 per cent. solutions of urea will cause intravascular haemolysis, but if by the addition of sodium chloride this solution is made isotonic with the blood plasma, no haemolysis will occur.

Saponin and some other glucosides are intensely haemolytic. It is believed that this is due to the action of these glucosides upon the cholesterin of the corpuscle, and it has been shown by Ransom that cholesterin can protect the corpuscles from saponin. The action of these substances occurs in three steps—first the envelope is affected, next the pigment escapes, and finally the electrolytes pass out.

3. Haemolysis may be produced by the action of toxic phytalbumoses, such as ricin and abrin, bacterial toxins such as tetanolysin, and by some constituents of snake venom.

4. Certain drugs may cause haemolysis, notably chlorate of potash, nitrites, phenylhydroxylamine, and bodies of the phenacetin group.

5. It has for some time been well known that the serum of one animal may be haemolytic to an animal of another species. Transfusion of sheep's blood into the vessels of a man causes fever and haemoglobinuria, and Landois showed that this was due to a specific globulicidal action. The serum of a dog is haemolytic to rabbits, and that of a horse is haemolytic to guinea-pigs.

Belfanti and Carbone found that, on injecting the blood corpuscles of a rabbit into a horse, the serum of the horse became toxic to the rabbit. Bordet and Ehrlich and Morgenroth made further investigations, and, by injecting defibrinated ox-blood into rabbits, obtained a serum haemolytic to oxen.

### *History.*

Paroxysmal haemoglobinuria was first observed by Charles Stewart in 1794. Rayer, in his 'Treatise on Diseases of the Kidneys', published in 1841, gives a vague reference to the disease. Dressler, in 1854, published an account of an 'Intermittent Albuminuria and Chromaturia', the first satisfactory description of the disease. He pointed out that the urine contained only a brown amorphous pigment and that no blood corpuscles were to be found in it.

During the following decade, cases were described in England by Harley, Dickinson, Gull, Hassall, Pavy, and others. Hassall recognized that the pigment found in the urine was haemoglobin, and further that the disease was almost exclusively a cold-weather ailment. He accordingly named it 'winter haematuria'. Dickinson was of opinion that the disease originated in the kidneys.

With the introduction of refined methods of investigation and the use of the spectroscope the name 'haemoglobinuria' was definitely adopted. The title 'Paroxysmal Haemoglobinuria' was first suggested by Secchi. Ringer, in 1868, remarked that not only cold, but also a number of other causes might give

rise to this condition. Greenhow attempted to trace resemblances between paroxysmal haemoglobinuria and malaria. Wiltshire ascribed the condition to an autogenetic intoxication and suggested the name 'paroxysmal haemolysis'.

In 1881 Fleischer pointed out that severe exertion might cause paroxysms. In Strubing's patient, attacks were said to follow alcoholic bouts and excitement. Kast described a case in which prolonged exertion caused attacks, while cold was ineffectual. Prior found that both cold and exertion could produce paroxysms.

Many of the early hypotheses as to the causation of the disease were fanciful, and of purely historical interest. Some writers were of opinion that it was due to disease of the kidneys, nephritis or congestion. Pavy believed that a vaso-motor disturbance, acting upon the blood, caused congestion of the viscera, especially the kidneys. von Popper considered that the disease was due to a vaso-motor neurosis.

The relation between paroxysmal haemoglobinuria and malaria was in the early days a subject of much speculation, and it is possible that some of these earlier cases were really malarial haemoglobinuria and that the diagnosis of paroxysmal haemoglobinuria was not justified. The occurrence, in many cases, of syphilis as an antecedent was not recognized until later.

The credit of the discovery of the disease thus rests with Dressler, and the first description in English is by Harley. In the period following this, as has been seen, many cases were recorded in England and elsewhere. The first philosophical study of the disease was carried out by Murri of Bologna. Mesnet published the first French account of the disease. Chvostek, in 1894, made an exhaustive analysis of the literature of the subject, and investigated a number of cases under his care. More recently, the work of Eason in this country and that of Donath in Germany have broken entirely fresh ground and added considerably to our knowledge.

### *Notes upon Cases.*

Paroxysmal haemoglobinuria may occur at any age, but is rarely found in patients above the age of fifty. It is as common in children as it is in adults. The majority of the patients are males.

A haemoglobinuric patient is typically pale and anaemic, usually weak and ill-nourished. This is, however, by no means always true. Some patients, though pale, are powerful and well-built, and some are healthy-looking people with good complexions.

There are, in all cases, well-marked prodromal symptoms, which enable the patient to foretell an attack. These vary in different patients, but the most frequent are yawning, pains in the back spreading to the limbs, cramps, cyanosis, abdominal pain, and, less frequently, shortness of breath. There is, at the same time, a shivering and a feeling of cold, that prompts the patient to seek the warmest place within reach. In an hour or two, the patient passes dark-red or dark-brown urine, which on examination shows the spectrum of oxyhaemoglobin or methaemoglobin.

At the beginning of last year there were in Guy's Hospital three cases of paroxysmal haemoglobinuria, but unfortunately only one patient was con-

tent to stay under observation. He stayed in the hospital five weeks, and still comes from time to time to report. He is a man aged 36, of medium height, pale and anaemic but well-built. He has never been abroad. He is a casual labourer, finding employment principally in docks and river-side factories. Twelve years ago he was a pugilist of some note.

In 1895 he had syphilis, followed by slight secondary symptoms. In 1897 he had pneumonia. He is not a person of great intelligence, and it was difficult to obtain an exact history of the occurrence of haemoglobinuria. In 1900, while at work, he started shivering and became dizzy and had to stop work, but his urine was not altered. In the year following, while at work in dry dock, he had a similar attack, but this time it was followed by the passage of 'black urine'. Since then, he has been subject to attacks every winter. In the cold summer of 1907 he also had attacks. He volunteered a statement that when he felt cold, exertion did not produce warmth, but rather made him colder and colder until a paroxysm supervened. This has also been noticed by Eason.

In April, 1904, he was admitted into Guy's Hospital for 'haemoglobinuria and rigors'. There were severe gastro-intestinal symptoms, such as diarrhoea and vomiting. No urinary casts were found, nor were there physical signs of heart-disease. Probably these gastro-intestinal symptoms are due to polycholia, which as previously stated is a logical antecedent of haemoglobinuria. Although anaemic, and sometimes 'lemon-tinted', it is not stated in any of the reports that W. E. was jaundiced.

In the autumn of 1905 he was again admitted into the hospital, in very much the same condition. No physical signs of heart-disease were found.

After his discharge from the hospital on this occasion, he got into regular employment. In spite of occasional paroxysms, he did not seek medical advice, as he was unwilling to run the risk of losing his work. In the beginning of 1908, however, he found that his health in other respects was unsatisfactory, and, on February 25, he came up to the hospital and was admitted—in the height of a paroxysm.

In the receiving-room he presented many of the symptoms premonitory of an attack, such as shivering, yawning, pains in the back, and cramps. Half an hour after admission he passed dark-brown urine, and it was ascertained by means of the spectroscope that methaemoglobin was present.

It was found that he had aortic disease: systolic and diastolic bruits were heard in the aortic area, and a Flint's bruit was heard over the impulse. The lungs were emphysematous. The liver was not enlarged. An examination of the nervous system showed nothing abnormal: in this respect a great change was found six months later. This physical examination was made on the day after admission, after the termination of the paroxysm.

### *Experiments.*

W. E. remained in the hospital for five weeks, and during this time had six paroxysms. For the greater part of the time he was not confined to bed, but permitted to walk in the grounds, when the weather was favourable. When the day was sufficiently cold, a paroxysm could readily be induced by sending him into the open air: cold baths and such drastic measures were unnecessary.

Experiments upon the blood *in vitro* were performed with a view to finding whether a specific haemolysin was present, and to an investigation of the scope and mode of action of such a haemolysin, should its presence be proved. I can claim no originality for this research, as Eason has been over

the ground very thoroughly, and I have consequently been able to do little more than confirm his observations.

The apparatus used consisted of a rack of small sterilized test-tubes plugged with cotton-wool, an incubator at 37° C., and a receptacle filled with ice-water; a centrifuge and two saline solutions. These solutions were—(1) a solution of potassium oxalate, 0·25 per cent. in a 0·85 per cent. sodium chloride solution, hereinafter referred to as the oxalate solution, and (2) a 0·85 per cent. sodium chloride solution, referred to later as the saline solution.

Blood was obtained from the finger or from the lobe of the ear. The first series of experiments was performed with blood obtained during an interval between two paroxysms.

(1) Blood from W. E. was mixed with twice its volume of oxalate solution and divided into two portions. The first portion was put into ice-water for half an hour and then into the incubator for twelve hours. The second portion was put into the incubator for twelve hours. Haemolysis occurred in the first tube, but not in the second. Similar control experiments were done with my own blood and haemolysis did not occur in either tube.

Similar experiments were performed on the following day with this modification. It was a cold day (42° F.) and the patient went out into the cold air. A test-tube containing the oxalated blood was also put in the open and subsequently—after warming—haemolysis took place *in vitro*. The patient also had a paroxysm. Thus the same conditions of temperature produced haemolysis simultaneously *in vivo* and *in vitro*.

Another specimen of oxalated blood was put in the ice-water for half an hour, and then left in the test-tube rack all night, and not in the incubator. No haemolysis took place, until after a subsequent warming in the incubator. This shows that a cold stage and a warm stage are both necessary for the production of haemolysis.

On another day, another portion of blood was taken and mixed with oxalate solution, as above. It was divided into two parts, *A* and *B*. *A* was put into ice-water for half an hour and then centrifugalized. The serum (*a*) was drawn off. The corpuscles (*b*) were washed free of serum in the following way. Saline solution was added until the original bulk of liquid was equalled. The mixture was then shaken and again centrifugalized. The clear fluid was poured off and more saline solution was added. The mixture was again shaken and centrifugalized. The clear fluid was then poured away, and the process repeated once more. By this means the last traces of serum were washed away.

The second portion, *B*, was not put into ice-water, but centrifugalized at once. Serum (*c*) and corpuscles (*d*) were separated and washed as above.

1. *a* (iced serum) and *b* (iced corpuscles) were added together, and put in the incubator for twelve hours. Considerable haemolysis followed.

2. *a* (iced serum) and *d* (un-iced corpuscles) were added together, put into ice-water for half an hour and then incubated. No haemolysis followed.

3. *c* (un-iced serum) and *b* (iced corpuscles) were added together and incubated for twelve hours. Haemolysis followed.

4. *b* (iced corpuscles) with a suitable bulk of saline solution was put into the incubator for twelve hours with no haemolysis.

The first and last of these experiments, (1) and (4), show that, although the first stage of haemolysis is effected during the cold stage, yet corpuscles and serum must remain in contact during the warm stage if haemolysis is to follow. That is to say that, during the cold stage, the corpuscles are acted upon in such a way as to render them vulnerable to the action of some component of the serum in the warm stage.

The second experiment (2) was uncertain in its results. On this occasion I found that no haemolysis occurred. On repeating the experiment on other days, at one time there was a slight degree of haemolysis, and at another time haemolysis was quite marked. The explanation of this may be that during exposure to cold, the erythrocytes rob the serum of one of its components. This component renders them vulnerable to that other component of the serum, which in the subsequent warm stage completes the process of haemolysis. After exposure to cold in company of the corpuscles, the serum is wholly or in part robbed of one of its components. If no trace of this component is left, the serum becomes inactive by exhaustion and, if added to red corpuscles, will not produce haemolysis when incubated, unless the corpuscles themselves have, from a previous icing, had the opportunity of linking themselves to the missing component. If on the other hand—this is the more common condition—this component has not been completely abstracted, then the experiment will end in haemolysis. The degree of haemolysis possibly bears a rough proportion to the activity of the serum.

The third experiment (3) shows that for the completion of—to use a loose term—the warm stage of haemolysis, it is not necessary for the component of the serum which acts during this stage itself to have been exposed to cold.

If the terminology of the immunity hypothesis be applied to these experiments, they may be interpreted in the following way. In paroxysmal haemoglobinuria, there exists in the serum a specific haemolysin. This haemolysin is made up of two constituents, amboceptor (intermediary body) and cytase (alexine or complement). When the blood is exposed to a low temperature the amboceptor becomes linked to the corpuscle. The cytase is active only at the body-temperature and cannot act upon a corpuscle alone, but only upon the corpuscle + amboceptor group. Therefore, when in an incubator the blood is kept at the appropriate temperature a destructive combination of the three bodies, corpuscle, amboceptor, and cytase, occurs.

During another interparoxysmal period, a third series of experiments was performed. A portion of blood from W. E. was mixed with oxalate solution, and divided into two portions, *A* and *B*. The first portion, *A*, was put into ice-water for half an hour and then centrifugalized into (*a*) serum and (*b*) corpuscles as before. In the case of *B*, the ice-water stages were omitted, but (*c*) serum

and (*d*) corpuscles were similarly separated. A specimen of normal blood, *C*, was taken from my own finger and divided by the centrifuge into serum (*e*) and corpuscles (*f*).

1. *a* (iced serum of W. E.) was exposed to a temperature of 56° C. for half an hour. It was then added to *b* (iced corpuscles of W. E.) and put into the incubator for twelve hours. No haemolysis occurred. Then *e* (serum of H. M.) was added and the tube was again put into the incubator for twelve hours. Haemolysis ensued.

2. *c* (un-iced serum of W. E.) was exposed to a temperature of 56° C. for half an hour. It was then added to *d* (un-iced corpuscles of W. E.), and the tube was put into ice-water for half an hour, and then incubated for twelve hours. No haemolysis occurred. *e* (serum of H. M.) was added, and the incubator stage repeated. Haemolysis then occurred.

3. *c* (serum of W. E.) and *f* (corpuscles of H. M.) were added together, put into ice-water for half an hour, and then into the incubator for twelve hours. Haemolysis occurred.

4. *e* (serum of H. M.) and *d* (un-iced corpuscles of W. E.) were together put into ice-water, and then incubated for twelve hours. No haemolysis took place.

The first and second experiments of this series show that the cytase is destroyed and rendered inactive by exposure to a temperature of 56° C. for half an hour. But experiment (2) shows that this temperature does not destroy the amboceptor. Further, the two experiments show that the cytase is not peculiar to the blood of haemoglobinurics, but occurs also in the serum of normal blood. The last experiment (4) shows that the amboceptor does not occur in normal blood, but only in that of affected persons. The third experiment (3) shows that this haemolysin can destroy normal corpuscles, and consequently that it is not necessary to assume that there is any diminished power of resistance in the corpuscles of the haemoglobinuric.

The conclusions to be drawn from these three series of experiments are as follows. There exists in the serum of haemoglobinuric patients a specific haemolysin, consisting of two portions, amboceptor and cytase. The cytase is destroyed at a temperature of 56° C., but the amboceptor resists this temperature. The cytase is a constituent not only of haemolytic, but also of normal serum, but the amboceptor occurs only in the serum of affected persons. This specific haemolysin is isolytic as well as autolytic; that is to say it is capable of producing haemolysis, if added to normal blood. It is not therefore necessary to assume any specific vulnerability in the corpuscles of the haemoglobinuric.

During the time that W. E. spent in the hospital, six paroxysms occurred, and I was able to perform a few experiments on the process of haemolysis *in vitro* with blood obtained during one or other of these paroxysms.

Blood was obtained from W. E. at different stages of the paroxysm, and allowed to clot in a small hermetically sealed tube. In a severe paroxysm, it was found that a pink tinge could be observed in the serum an hour after the first exposure to cold, and this persisted for perhaps an hour to two hours after

the first appearance of haemoglobinuria. In less severe paroxysms, the pink tinge of the serum disappeared before any haemoglobin appeared in the urine.

In a severe paroxysm, but before the appearance of haemoglobinuria, blood was obtained from W. E. and mixed with twice its volume of oxalate solution. It was placed in the incubator for twelve hours, and haemolysis occurred. Another sample of blood was taken at the same time as that required in the foregoing experiment, and allowed to clot in a tube. The serum showed no signs of free haemoglobin. The corpuscles had probably united with the amboceptor *in vivo*, as no cold stage was required *in vitro* to produce haemolysis.

Eason obtained blood from one of his patients at the beginning of a sharp paroxysm, mixed it with an equal part of oxalate solution, and centrifugalized quickly. There was no apparent haemolysis. The corpuscles were washed in the manner described above. He then treated some of his own blood similarly, and thus obtained a normal oxalated serum. This normal serum was then added to the corpuscles, and incubated for twelve hours. Haemolysis occurred, showing that union of corpuscles and amboceptor had occurred in the vessels of the patient, and that the addition of cytase was sufficient to produce haemolysis on incubating.

Further, he added the serum of the patient, obtained at the same time as the foregoing experiment, to his own normal washed blood corpuscles. No haemolysis occurred after twenty-four hours in the incubator. But another similar preparation was placed in ice-water for half an hour, and then incubated. In this case haemolysis did occur, showing that, although the serum had given up amboceptors to the corpuscles, as shown in the previous experiments, yet it retained a sufficiency of amboceptors to produce further haemolysis on a return to suitable temperature conditions. This experiment suggested to Eason the following hypothesis: the limitation of the paroxysm may not be determined by the using up of the intermediary bodies (amboceptors), nor even by the formation of anti-intermediary bodies, but simply by a restoration of the body to temperature conditions which do not further favour the anchoring of intermediary bodies to the cells.

Eason performed a large number of experiments with serum obtained from his patient by means of blisters, and found that the blister serum was haemolytic under the same conditions as the blood serum. On one occasion, I applied a blister to W. E. in the hope of performing experiments with his blister serum, but he resented the process so much that I was obliged to abandon them.

These experiments all lead to the conclusion that there is, in the blood of haemoglobinurics, a potential haemolysin, called into activity by those influences which have been already referred to as the causes of paroxysms. Of these, cold is the most prominent. This haemolysin is composed of amboceptor, the characteristic element, and cytase, which occurs also in normal blood. Cytase is only active at or near the body-temperature, and is destroyed at 55° C. Amboceptor can act at 0° C., and is not destroyed by heating to a temperature of 55° C.

*The Corpuscles.*

After a number of paroxysms have occurred in quick succession, the condition of the patient is one of anaemia, and various enumerations have been carried out with a view to finding the nature and extent of changes in the blood-corpuscles. In the case of W. E., I found that the number of red corpuscles per cubic millimetre was, on the morning of March 20, 4,000,000. At 1.30 p.m. he was sent out for a cold walk, and another blood-count was made at 4 p.m. The number was then 3,400,000. At 4.30 p.m. he passed ten ounces of urine containing methaemoglobin. He passed more darkly stained urine at 6 p.m. and again at 8 p.m. At 10.30 p.m. he passed clear urine, and at 11 p.m. another blood-count was performed. It was then found that the number of red cells was 3,200,000 per c.mm. The next morning, at 10.30 a.m., they amounted to 3,600,000 per c.mm. Three days later, it was found that they had increased to 3,900,000, and on September 20, when six months had passed without a paroxysm, the number was 4,500,000.

The haemoglobin percentage as estimated by Gower's instrument did not quite keep step with these changes. On the same day, at 11 a.m. the haemoglobin was 80 per cent.; at 4 p.m., 75 per cent.; at 11 p.m., 65 per cent.; and on the next morning, 70 per cent. Kobler and Obermeyer in their enumerations obtained the following figures:—

| | *Red corpuscles per cubic millimetre.* | *Haemoglobin by Fleischl's instrument.* |
|---|---|---|
| Before attack . . | 3,589,000 | 90 % |
| During attack . . | 2,890,000 | 85 % |
| After attack . . | 3,810,000 | 80 % |

These results also show that the young red cells are relatively deficient in haemoglobin. Mannaberg in his case discovered a most profound anaemia. His figures were:—

| | *Red corpuscles.* | *Haemoglobin.* |
|---|---|---|
| In attack . . | 895,000 | 45 % |
| 1st day after . . | 1,500,000 | 45 % |
| 2nd day after . . | 3,500,000 | |
| A fortnight later . | 4,390,000 | 60 % |

Bristowe and Copeman carried out a series of enumerations on a case in St. Thomas's Hospital and found the same rapid fall in the number of red cells during an attack, with an equally rapid rise when the attack was over, showing that in these cases there is a remarkably rapid reconstitution of corpuscles, although the young corpuscles are very deficient in haemoglobin.

In cases of paroxysmal haemoglobinuria in children these variations are even more extreme, and the return to the normal is more strikingly rapid than it is in adults. The effect of a prolonged stay in hospital, with an equable tempera-

ture and favourable surroundings, has a very beneficial effect upon these patients. Burckhardt reports the case of a boy six years old, who was for six months in hospital, during which time the number of erythrocytes per cubic millimetre increased from 1,500,000 to 6,000,000, while at the same time the haemoglobin percentage rose from 26 per cent. to 70 per cent.

Examination of blood films, fixed and stained, brings further evidence of the profound disturbance of the erythrocytes. Films of the blood of W. E., obtained before a paroxysm, show that the red cells are uniform in size and shape, and that the haemoglobin is equally distributed between them. After a paroxysm, it is found that they present all manner of sizes and shapes, microcytes and megalocytes (a few), crenated cells, lenticular cells, dumb-bell shapes and the like. As regards their haemoglobin content, all stages are found between the deeply-charged cells heavily laden with haemoglobin and the 'ghosts' (Ponfick's 'Schatten'), which have lost all their pigment. Globules of haemoglobin are seen free in the serum, some of them attached to ghosts, others floating free. On two occasions I was able in stained films to see basophil punctuation in the red cells similar to that observed in pernicious anaemia and some other conditions, such as lead-poisoning. In one film, obtained on the day after a paroxysm, there were three nucleated red corpuscles. In wet preparations, it is observed that the red cells have little or no tendency to form rouleaux.

In the preparation of films from the blood of W. E. during, or shortly after, a paroxysm, I found a peculiar difficulty in fixing the film to the slide. The ordinary heat-fixation was quite unsatisfactory; osmic acid was little better, and the alcohol and ether method was the most successful of the means I tried. Stephens and Christopher, in their observations upon black-water fever, found a similar 'loss of stickiness'.

I did not make any observations upon the specific gravity of the blood, but it would appear from the observations of Copeman that this varies directly with the number of red cells.

My enumerations of the white cells of W. E. gave the following results:—

| | *Leucocytes.* | *Neutrophil.* | *Acidophil.* | *Small lymphocytes.* | *Large lymphocytes.* |
|---|---|---|---|---|---|
| Commencement of a paroxysm . | 9,500 | 54 % | 2 % | 20 % | 24 % |
| After a paroxysm | 11,000 | 68 % | 1 % | 20 % | 11 % |
| Three days after a paroxysm . | 10,000 | 62 % | 2 % | 22 % | 14 % |
| Six months after a paroxysm . | 9,500 | 55 % | 1 % | 25 % | 19 % |

This table shows that, during a paroxysm, there is a marked increase in the neutrophil cells, and a less marked in the small lymphocytes. The large lymphocytes, on the other hand, undergo a marked decrease, and, after a paroxysm, the conditions return slowly to the normal. The percentage of

large lymphocytes was always above the normal, a condition similar to that which is met with in cases of recent malarial infection.

Mattirolo and Tedeschi publish a case in which there was a leucocytosis before the paroxysm, and a diminution in the number after a paroxysm. In Eason's case, it was found that there was a reduction after a paroxysm.

Donath in 1904 published a case in which the paroxysm was followed by a diminution in the number of leucocytes, thus agreeing with Mattirolo and Tedeschi.

Silbermann was of opinion that there was, in paroxysmal haemoglobinuria, a destruction or destructive change in the white cells, and that this change was the chief cause of the symptoms attending the paroxysm.

Ruziczka in his observations upon immunity has observed that, in the presence of the intermediary-body, the phagocytes are stimulated to great activity in attacking the erythrocytes. He found that, after immunizing guinea-pigs to fowl's blood, the phagocytes were able to destroy the red cells without previously absorbing them, but simply by fixing themselves to one point and nibbling away the cell-substance. Levaditi, Savtchenko, and Grüber also found that erythrocytes loaded with intermediary-body are very readily absorbed by the white cells.

Eason in one of his cases of paroxysmal haemoglobinuria found the same exaltation of the phagocytic function and, by analogy with the results of the above observers, attributed it to the presence of intermediary-body.

Bordet was of opinion that the cytases or complements which, in the defence of the body against foreign cells, attacked these cells when they were rendered vulnerable by the amboceptor group, were the products of leucocytes. It has been seen above that, in paroxysmal haemoglobinuria, a similar toxin is present, and the parallelism between the experiments performed *in vitro* and these observations upon phagocytosis in the presence of intermediary-body is obvious. The explanation must be, that a leucocyte loaded with cytase is attacked by an erythrocyte loaded with amboceptor and the haemolytic cycle is complete. In the interparoxysmal periods leucocyte and cytase, amboceptor and erythrocyte are circulating in the blood, and it is not until conditions arise which cause the linking of the amboceptor to corpuscle that the cytase can come into action.

Eason examined microscopically a preparation which showed the action of the haemolytic serum upon normal blood. In this slide, after the preparation had been left for an hour in a moist chamber, he observed (1) no formation of rouleaux, (2) variation in the size of cells, (3) poikilocytosis, some of the cells becoming lenticular, (4) a pinkish change in the pigment, (5) no crenation. In a normal control left in the same moist chamber he found (1) general formation of rouleaux, (2) no variation in size of cells, (3) no poikilocytosis, (4) no change in the pigment, (5) distinct crenation. Globules of haemoglobin may in some cases be seen free in the serum, or irregularly distributed in the cells. Therefore it appears that the leucocytes take an active part in attacking the red corpuscles,

and the essential factor in the haemolysis may be a change in the relations between the red and the white corpuscles.

A pink staining of the plasma precedes the discoloration of the urine. Blood drawn from a finger very shortly after the commencement of exposure to cold shows this; and, on the other hand, at the end of the paroxysm, while the urine is still dark coloured, the blood serum has returned to its normal condition.

In a paroxysm excited by some severe local exposure, such as immersion of the feet in cold water, it is found that the blood at or near the site of exposure undergoes haemolysis before the blood in some distant part. In blood obtained from a skin puncture in the neighbourhood of the ankle, the serum was quite pink, while a similar specimen obtained from the arm yielded a normally coloured serum. It was further found that, even in paroxysms provoked by a general exposure, the process commenced in the extremities, and a pink serum could be obtained from fingers, toes, and ears at a time when that obtained from some more central position was still normal. This observation makes clear two facts: first, that the circulation in these patients is remarkably slow, and secondly that haemolysis undoubtedly takes place in the vessels themselves and not in any of the viscera. Hunter points out this important difference between the pathology of pernicious anaemia and paroxysmal haemoglobinuria, namely, that in the latter disease the blood-destruction takes place in the vessels and in the former it takes place in the liver.

Before a paroxysm, the serum does not differ in colour from that of a normal person. On the day following a paroxysm, the yellow tint of the serum is deeper than the normal tint. This is probably due to an excess of lutein, the normal pigment of the serum. On a spectroscopic investigation, no absorption bands are revealed. This excess of lutein has also been observed by Stephens in cases of black-water fever. Its significance is not known.

The blood of W. E. was twice submitted to bacteriological investigation. Blood was drawn from a vein in the arm and attempts made to cultivate from it. In both cases a negative result was obtained. Cattle and sheep suffer from an endemic haemoglobinuria, and in this disease a specific haematococcus has been isolated. On the other hand, no organism has been found present in the haemoglobinuria of horses.

To sum up the blood changes in paroxysmal haemoglobinuria, it is found:—

1. That in a paroxysm, there is a profound destruction of red cells, followed by an equally rapid re-formation when the paroxysm is over. Evidences of this destruction are obtained, not merely from enumerations, but also from the modifications of the surviving red corpuscles, e.g. poikilocytosis, hypochromasia, and so on.

2. Although reconstitution of blood after a paroxysm is rapid, yet a quick succession of paroxysms strains these powers of reconstitution, and will produce a profound anaemia.

3. There is a slight increase in the number of leucocytes during a paroxysm,

especially of the neutrophil corpuscles. The leucocytes appear to participate actively in the process of destruction of red corpuscles.

4. The serum before a paroxysm is normal and after a paroxysm contains excess of lutein. Soon after exposure to cold, the serum in the extremities becomes pink, and this is followed by a general haemolysis. The serum returns to its normal colour, before the urine is free from its paroxysmal pigments.

### *The Urine.*

During the intervals between paroxysms the urine passed by W. E. was normal in every respect. 60 to 80 oz. were passed in twenty-four hours; the reaction was usually faintly acid and the average specific gravity was 1·016. The colour varied from a pale straw colour to a deep amber and there was little or no sediment. No albumin was present.

The most obvious change during a paroxysm was the change of colour from amber to dark brown or occasionally to dark red. The colour is very intense, and the patient himself called it black. A spectroscopic examination of the urine showed the four absorption bands characteristic of the spectrum of methaemoglobin or of acid haematin. These two substances possess similar spectra, and the only test by which they can be distinguished from one another is given by the addition of a reducing substance such as ammonium sulphide. Methaemoglobin then is replaced by reduced haemoglobin, and acid haematin by reduced alkaline haematin, and these bodies have different spectra. By means of this test, it was found that the colour was due to methaemoglobin. On one occasion only was acid haematin present.

This brown colour was present when the urine was acid. In neutral urine, the colour was red, and this was due to the presence of oxyhaemoglobin. Further, if the patient was made to micturate frequently, the urine thus passed was found to be red and to contain oxyhaemoglobin. Therefore it is probable that the pigment passes from the kidneys into the bladder in that form.

It is known that oxyhaemoglobin in the presence of an acid becomes changed into methaemoglobin, and, if the process be allowed to continue further, into acid haematin. So that it is highly probable that the colour of the urine depends upon its reaction and upon the time that it remains in the bladder; a long stay in the presence of a highly acid urine changing oxyhaemoglobin to methaemoglobin or even into acid haematin.

Dr. Robert Druitt, who was himself a sufferer from this disease and has left behind him an exceedingly graphic account of his experiences, mentions that his urine was at times chocolate coloured, at times normal in colour but with a heavy chocolate coloured sediment, and at times arterial-red in colour, alkaline and intensely irritating. Murri describes a case in which the urine during a paroxysm was neutral in reaction. The colour of the first specimen passed was that of malaga. A later specimen was chianti-coloured.

I next precipitated the blood pigments from the urine and, after filtration, examined it spectroscopically, expecting to find a large quantity of urinary pigments, indicative of increased activity on the part of the liver, but found much less than the normal quantity. Eason found a similar deficiency of the urinary pigments and concluded that, in a paroxysm, the liver, far from being overtaxed, was doing less than its usual work.

During a paroxysm there was a slight decrease in the amount of urea excreted. This agrees with the observations of Prior, Fleischer, and others. Gillespie, on the other hand, found an increase in the quantity of urea. It is also stated by most authorities that the total nitrogen in the urine is diminished. Eason, moreover, found that the percentage of urea nitrogen, which during the intervals was 83·5, the normal figure, rose during a paroxysm to 99·6 per cent. and fell again on the day after the paroxysm to 86·4 per cent.

The phosphoric acid is diminished, and Murri and others have found that, in spite of the extensive cell-destruction, there is no increase in the quantity of chlorides.

From these observations it appears that there is a slight diminution in the excretion of waste products. But cold and over-exertion, the agents in the production of a paroxysm, would both increase the waste products in a normal individual: cold by causing increased metabolism in order to maintain animal heat, and exertion by the result of muscular activity. So that there is apparently a retention of waste products during a paroxysm.

There is no change in the quantity of urine passed, but in most of the paroxysms there was a tendency to frequent micturition. The urine was slightly more irritating than at other times. This was especially noticeable on the occasions when the urine was alkaline and consequently of a bright red colour.

In the intervals between the paroxysms, there was little or no sediment, but the paroxysmal urine contained a heavy sediment, usually of a brownish colour. A microscopic examination of this sediment reveals the presence of a very few red corpuscles—perhaps one in two fields—an occasional ghost, and some pigment granules. There are also to be found granular hyaline and a few pigment casts, as well as a number of calcium oxalate crystals. In the urine of W. E. no epithelial casts were found, but Murri found them in one of his cases.

Albumin appears in the urine at a very early stage in the paroxysm, before the colour is changed. It also persists after all the haemoglobin has been discharged, even for two or three days after a paroxysm. In the case of a child, who was in the hospital in January of this year, it was found that albuminuria persisted for four or five days after a paroxysm. In no case on record is there a history of persistent albuminuria.

Sometimes, in the words of Strumpell, 'Bei leichten Anfällen kann es nur zu Albuminurie ohne Hämoglobinurie kommen.' A mild exposure to cold will cause a moderate degree of haemolysis: the liver will effect the elimination

of the haematin moiety and the globulin will pass out through the kidneys. Globulinuria is, in these cases, a more precise term than albuminuria, as the proteid in the urine is pure globulin. Bristowe has felicitously described these abortive paroxysms as the *petit mal* of haemoglobinuria.

But paroxysmal globulinuria occurs in many cases, which have never suffered from the corresponding *grand mal*. The intermittent albuminuria that follows bathing and such exposure was described by Dr. George Johnson in 1873. Under the name of periodic or cyclic albuminuria, it is recognized as an exceedingly common condition in young adults. It occurs less frequently in schoolboys. Exercise, fatigue, and exposure to cold are the most commonly recognized causes. Although essentially an ailment of youth which may disappear with advancing age, it is now recognized that many persons so affected in their youth become later the subjects of chronic nephritis. No case is recorded in which periodic albuminuria of adolescence has gone on to paroxysmal haemoglobinuria in later life, and it is probable that the resemblance between the conditions is superficial, and does not imply any kinship between the essential pathological causes which underlie them.

*Effects of Cold: Cutaneous Manifestations: Temperature.*

Patients with paroxysmal haemoglobinuria are remarkably sensitive to external cold, and in the severer cases there is 'extreme difficulty in maintaining animal heat'. These are the words of a patient. The circulation is usually extremely sluggish, and there is a tendency to 'dying of the fingers' and similar discomforts. W. E. was a person of sallow complexion, but on exposure to cold his face became cyanotic, his lips blue: his skin generally became mottled and his fingers dead. Exercise had no warming influence; in fact, he said that work made him feel colder. Dr. Druitt has given a graphic description of his own sensations. The illness began at Cambridge in 1867, when the patient 'believed himself to have been poisoned whilst hanging over the once beautiful streams at the backs of the colleges, then polluted with sewage'. After a moment's exposure to a cold wind, the face would become blue and the point of the nose almost black. This was so marked, that it attracted the attention of passers-by. His ears were subject to frostbite, his fingers were continually dead, and he suffered from chilblains.

In W. E. I found that the capillary reflux on the back of the hand was three times as slow as in a normal person. At one observation the time of reflux in my hand was four seconds, and in the patient's hand twelve seconds. The reflux in the case of the child was complete in ten seconds, as compared with five seconds in a normal person.

But these are not the only cutaneous manifestations met with. Purpura, urticaria, and circumscribed oedema have been described. In a case described by Wilks, the patient was cyanosed, the hand was at first blue and painful, and later there was dry gangrene of the fingers.

It has been already remarked that the sequence of events within the blood-vessels cannot be deduced from the behaviour of blood *in vitro*. Donath states that the processes are at least analogous: 'Durch Abkühlung und folgende Erwärmung des Hämoglobinurikerblutes *in vitro* erhält man ein Paradigma des durch Kälteeinwirkung verursachten Anfalles.' But apart from the fact that the corpuscles so treated become, from the very methods of the experiment, unstable, it is obvious that the circulating blood is in no case directly exposed to this extreme of temperature. In one of Copeman's cases, it was found that exposure to a temperature of 51° F. would cause a paroxysm—a temperature that was usually without effect upon the blood contained in a test-tube.

The influences of external cold may reach the blood within the vessels in two ways. It may directly chill the blood at or near the surface—say, within a range of two millimetres from the surface—or it may act indirectly, through the nervous system, sending impulses along a path analogous to, if not identical with, the vaso-motor arc.

If this latter hypothesis be accepted, it follows that a contributory cause of the paroxysms may be found in the nervous system. Murri was of opinion that there was in these cases an abnormal excitability of the vaso-motor nerve centre and claimed support for this hypothesis from the associated evidences of vaso-constrictor spasms, urticaria, cyanosis, and so on. Further, in cases of paroxysmal haemoglobinuria due to causes other than cold, there is a similar reflex; inanition haemoglobinuria is caused by a reflex which starts from the walls of the stomach, and menstrual haemoglobinuria by one from the walls of the uterus, while after severe exertion a 'haemoglobinuric reflex' starts from the muscles and travels along the muscle sense fibres.

Murri considered that haemoglobinuria in these cases was due primarily to a slowing of the circulation in the distal parts of the circulation. Chvostek administered amyl nitrite to one of his patients, and found that if administered at the beginning of a paroxysm, it would mitigate or even inhibit the paroxysm. 'Es gelingt den Paroxysmus so zu beeinflussen, dass, wenn die Anwendung frühzeitig erfolgt, es bei den Prodromalsymptomen bleibt, und dass die Application, selbst in ausgesprochenem Paroxysmus, denselben zu coupiren vermag, und bewirkt, dass er ein abortiver wird.'

Chvostek performed an interesting series of experiments upon horses, in which he found that by stimulating the spinal cord in the cervical region he could produce haemoglobinuria.

The boundary between paroxysmal haemoglobinuria and Raynaud's disease is very vaguely defined, and the above remarks may seem perhaps more appropriate to the latter ailment. The symptom-complex that is characteristic of Raynaud's disease differs in degree only from that of paroxysmal haemoglobinuria. If the vaso-constrictor spasms form the most prominent part of the clinical picture, the diagnosis of Raynaud's disease is made; if these symptoms are subsidiary to the intermittent haemolysis, the alternative title is employed. Both conditions are rare, and it is impossible to regard their so

frequent co-existence as fortuitous. From collected statistics it appears that 6 per cent. of patients with Raynaud's disease pass haemoglobin in the urine; and on the other hand a large number of patients with paroxysmal haemoglobinuria suffer from localized asphyxias, more or less severe. The cutaneous vaso-motor reflex causes, in the one case, an abnormal constriction of the vessel walls, and in the other case an actual disintegration of the formed elements of the vessel-contents. It has been thought by some authors that the haemolytic toxin is secreted by the vessel-wall, but there is no direct evidence for this view. On the other hand, if the excretion of waste products does not increase *pari passu* with the over-production due to cold or exertion, or whatever has caused the paroxysm, it is logical to surmise that the waste products so retained, and brought into intimate relation with the formed elements of the blood, or with the vessel-wall, might with the co-operation of an unknown factor cause the disintegration of the former and consequent haemoglobinaemia, or the spasmodic constriction of the latter with resulting local asphyxia. And in the case of the disease now being discussed, this unknown factor is in all likelihood the potential toxin whose existence has been proved in some previously described experiments.

The degree of cold which suffices to fire this train, so to speak, varies in different cases. One of my patients, the most intelligent of the three, informed me that in his case a paroxysm always followed exposure to a temperature of 40° F. In one of Copeman's cases it is recorded that a bath of ten minutes' duration in water at 51° F. would produce an attack. The most common history given is that the initial paroxysm followed an exceptionally severe chill, and that subsequent paroxysms were the result of a much more trifling stimulus. W. E. passed haemoglobin in his urine for the first time after a very cold day's work in dry dock. Another patient recently in Guy's Hospital passed haemoglobin in the urine after an attempted suicide from London Bridge and a consequent severe chilling. A certain physician, now deceased, was seized with his first paroxysm of haemoglobinuria after a cold and wet day's fishing in Scotland. His second attack was also the result of a wetting in the Highlands, but thereafter these attacks would be evoked by some much more trivial cause—a moment spent in the open air without an overcoat, even the very trifling exposure involved in opening a window, would determine an attack. Concurrently with this increased irritability or instability of the blood corpuscles, there is an aggravation of the subjective symptoms caused by cold; in fact, the two phenomena would appear to bear a constant proportion to one another, so that a patient is usually able to know from his own sensations whether an attack be imminent or not. It has been seen, from the account of Dr. Druitt's case, that the subjective phenomena form no small part of the sufferings of these patients.

The mouth-temperature of W. E. during the interval was usually between 97° and 98° F., and did not vary beyond those limits except during a paroxysm. At the commencement of an attack, there was a depression of temperature to

96° or 96·4°, and this was followed by a rapid rise of temperature to 101° or 102°. The maximum temperature usually coincided with the first appearance of pigment in the urine. After this the temperature fell gradually during the next two or three hours to 98°. After one paroxysm, the most severe that he experienced while in the hospital, the temperature fell to 96° and there was then a slight secondary rise to 99°. In the case of my other patient, the temperature did not rise above 100°. In about half of the cases described, there is a marked rise of temperature, synchronous as a rule with the height of the paroxysm, and this instability of temperature is specially marked when the disease occurs in children. In extreme cases, the temperature will, after a preliminary fall to 95°, rise in three hours to 104°. On the other hand, in many cases, extensive haemolysis occurs, and yet the rise of temperature is trivial.

Although it must not be overlooked that the records of cases in which the rise of temperature is most marked come principally from the earlier literature, and it is possible that there may have been a confusion of diagnosis, yet even in the most recent cases a temperature of 101° or 102° is the rule rather than the exception. It is probable that the rise in temperature is due both to increased heat production from increased metabolism, and to diminished heat loss due to the ischaemic condition of the skin. In this connexion, however, I must mention some rather paradoxical observations of Murri on the surface temperature during an attack.

He found that if his patient Bertozzi and a healthy person were exposed to the same atmospheric conditions, there was considerable divergence between the ratio of skin temperature to body temperature in the two cases. These differences were specially marked if they were exposed to a degree of cold sufficient to induce in Bertozzi a paroxysm. Both patient and healthy subject had their feet immersed in cold water for a quarter of an hour, and then the foot-bath was withdrawn. It was found that the surface temperature in the extremities, hands, feet, and so on, fell more in the case of Bertozzi than in the normal person. In some other positions, however, the surface temperature was higher in Bertozzi than in the other, and during the two hours following the experiment the temperature in these positions rose higher and higher. These positions were the back of the thigh and the small of the back. Murri's explanation of these phenomena is, that there is in haemoglobinurics a greatly increased heat production, and that the skin in the areas which lie over the great muscle-masses—the principal sites of heat-production—becomes consequently warmer than the corresponding areas of skin in a normal person under like conditions.

### *Morbid Anatomy.*

Paroxysmal haemoglobinuria is not dangerous to life. There is no record of any uncomplicated cases which have proved fatal. Occasionally, however, general tuberculosis or aortic disease may supervene, and I have been able

to find accounts of four post-mortem examinations. Murri's patient, Isaia Giovannini, died in 1877 of general tuberculosis. Tubercles were found widely distributed. The kidneys were hyperaemic, there was an excess of interstitial tissue unevenly distributed, and the cortex was hypertrophied. The epithelium of the convoluted tubules showed signs of degeneration. There was a peculiar congenital displacement and malformation of the right kidney. The lymphatic glands round the aorta and the vena cava were much enlarged.

Three days after the above autopsy took place, Demarchi Clemente died at Pavia. He had suffered from 'emoglobinuria dal freddo' for five years. The autopsy was performed by Stefanini with the assistance of Golgi. The arteries were atheromatous. The liver was quite normal, but the spleen was nearly twice the normal size. The kidneys were enlarged; the capsule stripped readily. The cortex was easily lacerated and the surface was marked with dark rose points. The medullary pyramids were hyperaemic and showed distinctly many red striae. Microscopically he found 'una leggere nefrite diffusa e specialmente interstiziale'. The patient died from aortic disease and it is probable that these were 'cardiac kidneys'.

Prior reports an autopsy in which nothing remarkable was found. Widal describes a deposit of pigment in the kidneys similar to that found in cases of malarial cachexia by Kelsch and Kiener.

The organs that demand most attention are naturally the kidneys. It was thought first that blood-pigment appeared in the urine as a result of morbid changes in the kidney,—that the disease was local. When the presence of free haemoglobin in the circulating blood was discovered, the problem became much more difficult. In a paroxysm, albumin and haemoglobin are found in the urine. Granted that they are derived from the destruction of erythrocytes, how do they contrive to traverse the renal filter? The molecule of haemoglobin may pass more easily than that of globulin through the filter, yet even then it is difficult to understand how it traverses the healthy kidney. It is true that in the two autopsies reported by Murri there was, in point of fact, some degree of nephritis. But on the other hand there is in the majority of reported cases strong evidence that the kidneys are healthy. In all three of my cases, the interparoxysmal urine was perfectly normal. In W. E., the paroxysmal sediment was frequently submitted to minute and careful examination and no epithelial casts were found. Epithelial casts are occasionally met with, and it is notable that they were found by Murri in the case of Giovannini. Perhaps in the small number of cases in which these have been found, there was some degree of nephritis. On the other hand, Litten in a study of haemoglobinuria in animals found that there was no nephritis, even though albumin persisted in the interparoxysmal urine.

In the case of Giovannini reported above, Murri was of opinion that there was an active hyperaemia in the glomeruli to which the ischaemia of the skin and obstruction from the large abdominal lymphatic glands contributed. Whether the pigment passes out in the glomeruli or by the convoluted tubules,

there are two views. Forsbach was of opinion that the haemoglobin passed out by the glomerular route and that the tubules did not participate in its elimination. Christomanos, on the other hand, found haemoglobin droplets in the tubular epithelium, while at the same time Bowman's capsule was quite free from haemoglobin. It is certain that the tubules frequently have their lumen entirely occupied with haemoglobin, as haemoglobin casts appear in the urine. Stempel states that, in paroxysmal haemoglobinuria, the pigment may block the tubules so as to cause uraemia, but I have been unable to find any record of such an event.

In the introduction to this paper, it was pointed out that haemoglobinaemia was followed by haemoglobinuria only when the liver was no longer able to cope with the abnormal conditions. A lesser degree of haemoglobinaemia was followed merely by greater activity on the part of the liver, an increased secretion of bile, and an increase in the urinary pigments. The scanty evidence afforded by post-mortem records shows that there is no organic change in the liver, but from clinical observation it is obvious that the liver does participate in the paroxysm. In the case of W. E., the liver during an interparoxysmal period was palpable about a quarter of an inch below the costal margin. At the onset of a paroxysm, it increased considerably in size and reached to a line an inch and a half or two inches below the costal margin. When thus enlarged it was slightly tender. This enlargement of the liver is mentioned in all the most detailed descriptions of cases, and in only one case is it specifically stated that the liver was not enlarged. It is therefore justifiable to assume that a paroxysm is accompanied by an enlargement of the liver in a typical case of the disease. But from the above 'overflow' theory of haemoglobinuria, it follows that a paroxysm should be accompanied by the clinical manifestations of an excess of bile; and it is certainly true that such alimentary disturbances as diarrhoea and bilious vomiting do not infrequently accompany a paroxysm. Jaundice is less common and would not occur unless some slight local obstruction was present. In none of my cases was jaundice present. One of them presented a lemon tint similar to that characteristic of pernicious anaemia. Occasionally during a paroxysm there was a peculiar yellowish discoloration of the sclerotic, due probably to free haemoglobin having penetrated into the lymph channels. In view of this apparent increase in the activity of the liver, it is surprising to find that very little urobilin is present in the urine. After haemoglobin has been removed by precipitation, the urine is found to contain only the merest trace of urinary pigment, and this has led competent observers to the opinion that the liver is not abnormally active during a paroxysm, that on the contrary there is an inhibition of its normal functions, and that this inhibition is a contributory cause of an attack. Against this view must be placed the fact that the faeces contain as large a quantity of bile as at ordinary times, and that alimentary disturbances due to hypercholia are of frequent occurrence.

In a large number of the cases reported it is stated that the spleen becomes large and hard during a paroxysm. This is a more obvious change than the

enlargement of the liver, and is mentioned in several accounts in which there is no reference to the liver. In the case of W. E., the spleen became doubled in size and easily palpable. The outline of the spleen could easily be seen if the abdomen was carefully watched during deep breathing. The organ was at the same time rather tender. In one of the reported autopsies, the spleen is described as large and hard, but no microscopic examination was made. It cannot be stated precisely what the significance of this enlargement of the spleen really is, but it may fairly be surmised that the products of blood destruction accumulate in that organ. Stempel is of opinion that the cell-wrecks (Zelltrümmer) are retained by the spleen, which swells in consequence. Reference has been made to the presence of ghosts in the blood during a paroxysm, but their fate has not been made clear. Such débris forms only a trifling portion of the urinary sediment. Litten, in his researches on some animals that had long suffered from haemoglobinuria, found in the spleen large cells rich in protoplasm and laden with haemoglobin droplets and damaged erythrocytes. He also found a hyperplasia of the red marrow. Analysis of the urine, as has been seen, shows that, in spite of the extensive cell-destruction that occurs during a paroxysm of haemoglobinuria, there is no increase in the elimination of chlorides, or of the total nitrogen. It has also been seen that the number of erythrocytes returns to the normal in a very short time after the end of an attack. All these facts combined would appear to point to a plausible hypothesis, namely, that the broken-down cells, ghosts and other débris—the killed and wounded left on the field after a paroxysm—are not completely destroyed and eliminated, but are collected in the spleen ready to be worked up again at the right time and place into new erythrocytes.

### *Syphilis and Paroxysmal Haemoglobinuria.*

The effect of syphilis upon the blood has received more attention from observers abroad than from those at home. The first research upon the subject was that of Wilbuscevick in 1874, who found in cases of syphilis that the red corpuscles were diminished and the white corpuscles increased. Upon the administration of mercury, the red corpuscles became at first more numerous and the white cells fewer, but when a certain point in the treatment was reached, the red cells again diminished. These opinions were confirmed by other observers. Bieganski found that in primary syphilis the number of red cells was not diminished, but their haemoglobin content was much reduced. The white cells became more numerous, the increase in the number of lymphocytes being particularly marked. After a course of treatment with mercury, the red corpuscles were increased and the haemoglobin percentage became normal. The number of white cells was diminished. Konried came to the conclusion that the haemoglobin moiety of the red corpuscle could resist the syphilitic virus less than the stroma. In untreated cases he observed that, with spontaneous involution of the symptoms of syphilis, the condition of the blood returned to

the normal. On the other hand, if the symptoms became aggravated, the quantity of haemoglobin became markedly reduced and severe syphilitic anaemia ensued.

Important work on this subject has been carried out by Murri and Justus. Their later researches throw a sidelight upon the relation between syphilis and paroxysmal haemoglobinuria and so point to a solution of the most important problem in the etiology of the disease.

Justus, by means of injection or inunction, administered mercury to a number of syphilitic patients, and observed the consequent variations in the percentage of haemoglobin. He found that, in an ordinary case of syphilis, the initial injection of $\frac{1}{6}$ milligramme of corrosive sublimate was followed by a 10 or 20 per cent. fall of haemoglobin. A second injection three or four days later was followed by a slighter fall, and after this a continuation of the treatment would slowly bring the haemoglobin percentage back to the normal figure. In cases of severe syphilis, or in cases where syphilis was complicated by an intercurrent disease, these falls in haemoglobin percentage after mercurial injections persisted for a longer period. If, in a severe case of syphilis, the blood is examined shortly after an injection of mercury, it is found that the destruction of corpuscles has been extensive enough to give the serum a pink tint. This reaction was considered by Justus to constitute an important test in doubtful cases of syphilis, but there has been considerable difference of opinion as to its usefulness.

Murri obtained blood by venesection from thirty syphilitic patients and divided each specimen into two portions. One series was allowed to clot at 20° C., while the other series was exposed to a temperature of 2–3° C. In the former series, the serum that separated out was normal in colour, but of those that had been exposed to cold, the serum in twenty-eight cases was pink. In some syphilitic patients, Justus was able to produce haemolysis by brief elastic constriction of the arm. In others he repeated the classical finger experiment associated with the name of Ehrlich. He placed an elastic band round the base of a finger and found that the stasis caused by this band had sufficed to produce haemolysis. No application of cold was necessary. Ehrlich made his patient put the finger, thus isolated, in ice-cold water for a quarter of an hour, and then allowed a specimen of blood obtained from the finger to clot. He found that extensive haemolysis had taken place. The experiment has been repeated by Boas, Copeman, and many others. Chvostek found, like Justus, that stasis without cooling was in some cases followed by haemolysis.

There is no doubt that the majority of patients with haemoglobinuria have had syphilis. A number give a history of syphilis; in others a systematic examination reveals traces of infection. It is noteworthy that some of the cases—a relatively large number—give a history of very severe secondary symptoms; and in a number of cases of paroxysmal haemoglobinuria, there exists also some definitely post-syphilitic lesion. In one case the patient suffered also from aneurysm; syphilitic arteritis is a frequent complication, and aortic

disease of specific origin has also been found in this series. W. E. was a notable example of how a number of these paraluetic conditions may co-exist. In February of last year, on admission to the ward it was found that he had aortic disease. His nervous system was also examined and nothing abnormal was found. In September, on readmission, locomotor ataxy was discovered in addition to his other troubles. He had in six months developed all the classical signs of this condition. The knee-jerks had disappeared, testicular sensation was absent, Romberg's sign was present, he had Argyll-Robertson pupils and abnormalities of gait were just becoming perceptible.

When paroxysmal haemoglobinuria occurs in children, there is usually an hereditary taint, and concomitant signs such as keratitis punctata, quiet effusion into joints, rhagades, and the like are described.

From the records of Guy's Hospital, and from the literature, I have collected 39 cases of paroxysmal haemoglobinuria; 30 of the patients were men. The age distribution was as follows: under 10 years there were 9 cases; between 10 and 20, 5 cases; between 20 and 30, 7 cases; between 30 and 40, 8 cases; between 40 and 50, 8 cases, and between 50 and 60 there were 2 cases. Acquired syphilis was an antecedent in 17 cases; 7 cases showed evidences of congenital syphilis; 7 cases were doubtful, and in 8 cases it is definitely stated that there was no history or evidence of a specific infection. The interval between the primary invasion of syphilis and the initial paroxysm of haemoglobinuria was in one case as short as 18 months, in another case as long as 20 years. The average interval is 7 years.

Stempel collected 77 authenticated cases of paroxysmal haemoglobinuria and found a syphilitic history in only 29 per cent. of them. The statistics quoted above show 60 per cent. It cannot be affirmed, therefore, that every case has a syphilitic origin, although in the majority of the cases the first cause of paroxysmal haemoglobinuria is without doubt syphilis.

What then is the connexion between these two diseases? The researches quoted at the beginning of this section show that the virus of syphilis has a profoundly deleterious influence upon the blood, and causes a distinct lessening of the stability of the erythrocytes. There are a number of ways in which this may have been brought about, and consequently there is prevalent a large number of conjectures. Most of these views it is at present quite impossible to prove or disprove. The oldest hypothesis is that syphilis so affects the blood-forming organs, that they produce red corpuscles of greatly diminished powers of resistance to hostile influences. Others, using a different expression, say that the effect of syphilis is to modify the stroma of the red corpuscles, so that it is no longer capable of holding firmly the haemoglobin moiety, that the link between stroma and haemoglobin is less firm than in the healthy person. Others say that there is a chemico-physical change, a modification of the cholesterin envelope or a diminution in the surface tension of the corpuscle. Chvostek has shown that simple mechanical shaking of the blood *in vitro* may cause haemolysis. All the hypotheses agree in substance, indicating that the red corpuscles

are more than usually vulnerable to attack, and postulating a hostile agency; but for the most part they are silent as to the nature of this agency. It has been shown in a previous section that there is in the serum of paroxysmal haemoglobinurics a potential toxin; but that the erythrocytes are abnormally vulnerable is doubtful. I found that the serum of W. E. when added to my own red corpuscles produced a haemolysis no less profound than that which followed its action upon the diseased corpuscles—that, in other words, the serum was not only autolytic but also isolytic. Perhaps—I had no means of exact measurement—the action upon healthy corpuscles was the more profound as there would not in healthy blood be any tendency to the formation of anti-autolysins. Eason has in his more recent work found that such bodies are actually found in the blood of haemoglobinuric patients.

It would be instructive to discover whether the serum in syphilitic persons is ever isolytic, whether it would have any deleterious influence upon healthy corpuscles. As far as I am aware no research of this kind has been carried out.

### *The relation of Paroxysmal Haemoglobinuria to Malaria, &c.*

It is usually stated in textbooks that, after syphilis, malaria is the most frequent antecedent of paroxysmal haemoglobinuria, but in my series of forty cases only two were associated with malaria. One of these malarial cases had also had syphilis, and in the other case syphilis could not be definitely excluded. An examination of the literature shows that cases which give a history of malaria were much more common thirty years ago than they are at the present day. Wickham Legg, writing in 1874, stated that one-third of the cases described gave a history of malaria: in 1908 malaria is recorded in 5 per cent. of the cases.

This discrepancy suggests that there was in the early days a confusion between paroxysmal haemoglobinuria and black-water fever. There is clinically a considerable resemblance between a mild attack of black-water fever and a severe paroxysm of haemoglobinuria; and further there is a number of changes in the blood, liver, and spleen, common to the two conditions. If it could be definitely proved that one case of authentic paroxysmal haemoglobinuria—'haemoglobinuria a frigore'—owed its origin to a malarial infection, then the affinity between the two conditions would be made closer. But there are no records of such a case.

Stewart's patient in Archangel in 1792 was successfully treated with quinine, but it is extremely doubtful whether this was actually a case of paroxysmal haemoglobinuria. Quinine was used in many cases more recently recorded, but without much success. Mercury has had better results.

For a short period in September, I administered quinine to W. E. in increasing doses, in order to ascertain whether it was possible to precipitate a paroxysm by such treatment, and in this I was unsuccessful. In a few days,

I had increased the dose so that the patient was taking thirty grains in twenty-four hours. This dose caused deafness and digestive disturbance, but it had no effect on the urine. I was then obliged to stop the administration as the discomfort produced was so extreme.

Rheumatic fever, enteric fever, and prolonged suppuration have been adduced in a few cases as possible antecedents of paroxysmal haemoglobinuria. Heredity, apparently, has played a part in a few cases. The case in which paroxysmal haemoglobinuria followed prolonged suppuration is suggestive in view of the fact that prolonged suppuration and syphilis are the two commonest causes of lardaceous disease.

## Conclusions.

1. Paroxysmal haemoglobinuria is the result of intravascular haemolysis.

2. This intravascular haemolysis occurs when the blood serum becomes autolytic. There is in the blood serum a potential toxin, composed of cytase and amboceptor, which becomes active under certain conditions.

3. The most prominent of these conditions is the application of external cold. In experiments *in vitro* it appears that direct application of cold will activate the serum. *In vivo* it is most probable that the application of cold sends impulses to the vessels by the vaso-motor arc—that the haemolytic reflex travels by the same path as the vaso-motor reflex.

4. Similarly in examples due to the less common causes, inanition, menstruation or exertion, haemolytic reflexes start from the stomach, the uterus, or the muscles respectively.

5. Variations in the severity of the paroxysm may depend upon variation in the excitability of the nerve centres. When these are unusually excitable, a paroxysm is more readily produced than when they are quiescent. This perhaps accounts for the fact that while the initial paroxysms in such patients are due to a very severe chilling, the subsequent paroxysms start from a much more trivial cause.

6. Paroxysmal haemoglobinuria and Raynaud's disease are closely related and the boundary line between the two conditions is indefinable. The vaso-motor disturbances characteristic of the latter disease are frequent in paroxysmal haemoglobinuria, and 6 per cent. of patients who suffer from Raynaud's disease pass haemoglobin in the urine.

7. A paroxysm is attended with great degeneration and destruction of the red corpuscles. The number of leucocytes is not greatly altered, but they participate actively in the process of haemolysis. Autolysis or heterolysis is always accompanied by exaltation of the phagocytic function; that is to say, in the presence of amboceptor, the leucocytes are stirred into great activity. It is probable that the leucocytes are the source of the cytases.

8. The serum of paroxysmal haemoglobinuria is isolytic as well as auto-

lytic: *in vitro* it can destroy the corpuscles of a normal person as well as those of a patient. It is not therefore necessary to assume any specific vulnerability in the red corpuscles in this disease.

9. After a paroxysm, the reconstitution of the blood is very rapid, and this, coupled with other observations which need not here be recapitulated, suggests that the products of cell-destruction are largely retained to form the raw material for a new generation of erythrocytes.

10. The ultimate source of the haemolysin is not known. Syphilis is a possible antecedent in a majority of cases, but the disease is not invariably syphilitic. Other antecedents, far less common, have been mentioned. In syphilitic patients generally, there is frequently a lack of stability in the blood which has a very suggestive resemblance to the conditions present in haemoglobinuria.

11. There are no gross organic changes in the abdominal viscera. The liver is enlarged during a paroxysm. The spleen also, possibly from an accumulation of waste products, becomes bigger. There is possibly a passive hyperaemia of the kidneys, but no inflammatory change.

12. Granted that, on the one hand, the blood circulating within the vessels contains a potential toxin which on the receipt of appropriate stimuli becomes actively haemolytic, and that on the other hand these stimuli, whatever their origin, reach the vessels by the vaso-motor nerve fibres, it would appear that there is still a missing link. The nerve endings are situated in the vessel-wall and have no direct communication with the blood itself. There is no evidence, histological or experimental, to support the view that a secretion is poured out by the endothelial cells, in response to secreto-motor stimuli.

Twenty-five years ago, an Italian author said that, in his opinion, paroxysmal haemoglobinuria was due to 'una discrasia sanguigna essenziale', and since his day there have been many sesquipedalian confessions of ignorance. Nowadays, it is possible to study with exactness paroxysmal haemoglobinaemia as it occurs in a test-tube, and it can fairly be claimed that the existence of a specific toxin has been proved. But there is still an unknown quantity, a gap in our knowledge of the sequence of events. No line of investigation hitherto suggested promises to give a solution of this problem. Until new methods or more perfected methods make such investigation possible, there will be no end to vague speculations, bricks without straw.

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# ON THE FREQUENT FAILURE OF THE URINE TO DECOMPOSE IN CASES OF PULMONARY TUBERCULOSIS

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In 1892 one of us pointed out that the urine of patients having pulmonary tuberculosis often remained acid for a very long time. Out of 182 specimens examined, 4 remained acid for over 100 days, 3 between 50 and 100 days, 14 between 30 and 50 days, 24 between 20 and 30 days, 19 between 15 and 20 days, 32 between 10 and 15 days, 50 between 5 and 10 days, and 36 less than 5 days. The acidity of the urine was roughly tested in a few cases and the results suggested that in this disease the acidity is sometimes unusually high. We have recently re-examined this matter and have confirmed the original observation, for, on looking at Table I, it will be seen that 29 separate specimens of urine collected, with one or two exceptions, for the whole twenty-four hours, were obtained from eight cases of pulmonary tuberculosis. Two specimens remained acid 2 days; 1, 3 days; 1, 5 days; 2, 8 days; 2, 10 days; 2, 12 days; 3, 15 days; 2, 16 days; 2, 17 days; 1, 19 days; 3, 20 days; 1, 25 days; 1, 27 days; and 1, 28 days. Specimen No. 3 (Case I) was still acid 115 days after it was passed. Specimen No. 5 (Case II) was still acid 135 days after it was passed. Specimen No. 8 (Case III) was still acid 108 days after it was passed. The specimen from Case VII was still acid 50 days after it was passed and No. 2 from Case VIII was still acid 27 days after it was passed. All the specimens on which the observations recorded in this paper were made, whether from sufferers from phthisis or any other disease, were collected during the cold weather of December, January, or February.

The acidity was always estimated by Folin's method. Twenty cubic centimetres of urine were measured into an Erlenmeyer's flask. To this 15 to 20 grms. of potassium oxalate were added to saturate it, and then two drops of phenolphthalein solution. A decinormal soda solution was then dropped in until a change of colour to a faint pink appeared, the flask being frequently shaken. A control flask containing a little of the same urine saturated with potassium oxalate was always prepared so that the first change to a slight pink in the first flask could be readily seen. As a rule two estimations of each specimen were made, and the result was not taken as correct unless the difference between the two estimations was not more than 0·1 c.c. of decinormal soda solution. The acidity was always expressed as the number of cubic centimetres of decinormal NaOH needed to neutralize 20 c.c. of the urine in question.

The acidity (see Table I) of nineteen specimens of urine from patients

suffering from other diseases than pulmonary tuberculosis was also tested, and the following figures show the acidity of these nineteen contrasted with that of the twenty-nine specimens from cases of pulmonary tuberculosis. In every case the urine was tested almost directly after it was passed. Our figures should not be compared with Folin's, for his represent the number of cubic centimetres of decinormal soda solution required to neutralize 25 c.c. of urine, ours the number necessary to neutralize 20 c.c. of urine, and the specific gravity of his specimens was higher than that of ours.

| 30 c.c. decinormal NaOH required to neutralize | *Cases of Pulmonary Tuberculosis.* | *Other Cases.* |
|---|---|---|
| 20 c.c. urine . . . . . | 1 | 0 |
| 11 c.c. . . . . | 1 | 0 |
| 10 c.c. or over, but under 11 c.c. . . . . | 2 | 0 |
| 9 c.c. „ „ 10 c.c. . . . . | 5 | 0 |
| 8 c.c. „ „ 9 c.c. . . . . | 5 | 0 |
| 7 c.c. „ „ 8 c.c. . . . . | 1 | 1 |
| 6 c.c. „ „ 7 c.c. . . . . | 7 | 3 |
| 5 c.c. „ „ 6 c.c. . . . . | 3 | 3 |
| 4 c.c. „ „ 5 c.c. . . . . | 1 | 9 |
| 3 c.c. „ „ 4 c.c. . . . . | 0 | 2 |
| 2 c.c. „ „ 3 c.c. . . . . | 3 | 1 |
| | 29 | 19 |

Thus we see that in twenty-five out of twenty-nine specimens of fresh urine from cases of pulmonary tuberculosis the acidity was 5 or more, but in only seven out of nineteen specimens of fresh urine from patients who were suffering from other diseases than pulmonary tuberculosis was the acidity 5 or more. Further, among those who were not sufferers from pulmonary tuberculosis, the acidity was never over 8, but of the specimens from those who had this disease the acidity was over 8 in fourteen, or virtually 50 per cent. It is particularly worthy of note that among those who were not suffering from tuberculous disease of their lungs two were cases of tuberculous peritonitis and one of Addison's disease. These three patients were responsible for nine specimens of urine; the acidity of one was 5, but the remaining eight were all under this figure. No other cases of tuberculosis in which the lungs were free happened to come under our notice while these observations were being made, but as far as the figures before us go they strongly suggest that this high acidity of the urine is not met with in tuberculous disease unless the lungs are affected. It will be noticed that the nine specimens of urine from the two cases of tuberculous peritonitis and the case of Addison's disease all decomposed quickly, three in four days, one in three days, four in two days, and one in one day.

As the cases of tuberculous disease of the lungs were all in-patients, and

therefore all severely ill, it was thought that perhaps the frequent failure of the urine to decompose was common to any severe infectious disease; so seven specimens of urine from four cases of acute pneumonia and three from a case of staphylococcal septicaemia were examined; but all ten specimens quickly decomposed, one remaining acid five days, three four days, three three days, and three two days. The highest acidity was 7·2, in three specimens it was 6 or over, in two it was 5 or over, and in four between 4 and 5. This somewhat high acidity is probably merely the result of the concentration of the urine, for all these patients had considerable pyrexia, but the acidity was far below that frequently met with in pulmonary tuberculosis, and none of these ten specimens of urine remained acid an unusually long while. It appears, therefore, we may conclude that the extremely slow decomposition of the urine frequently met with in some cases of tuberculosis of the lungs is, as far as is at present known, peculiar to that disease, in which also the urine is very often exceptionally acid.

We will now consider in more detail these two strange peculiarities of the urine of sufferers from pulmonary tuberculosis. Speaking generally, the more highly concentrated a urine is, the more acid it is; but we have just seen that five patients suffering from an acute febrile disease, and therefore passing concentrated urine, did not any of them pass urine as acid as is commonly the case in tuberculous disease of the lungs, and a reference to Case III is alone enough to show that in tuberculous disease of the lungs some other circumstance than concentration of the urine is necessary to explain its high acidity, for out of eight specimens examined, the acidity was never under 8, and twice it was 10, but the specific gravity never exceeded 1·014, and was in four specimens under 1·009. Again, we notice in Case III a specific gravity of 1·008 with an acidity of 10, and in Case IV the same specific gravity with an acidity of 2·5. It is true that in Case V, in which the very high acidity of 30 was attained, the specific gravity was 1·040, but from the considerations just given we are bound to conclude that some other factor or factors than specific gravity have to do with the high acidity of the urine seen in tuberculous disease of the lungs. No doubt the specific gravity plays its part, although a minor part.

It is well known that when oxidation is deficient in the body there is an accumulation of lactic acid which is excreted in the urine. We thought it just possible that as in these cases there was extensive disease of the lungs there might be deficient oxidation with a considerable excretion of lactic acid in the urine, and hence its high acidity, although such a view was unlikely, for the urine of the patients suffering from pneumonia did not show nearly as great acidity as those who had tuberculous disease of the lungs. The estimation of lactic acid in the urine requires special care, and we were fortunate in getting Mr. J. H. Ryffel, who has devoted particular attention to this, kindly to do some analyses for us. He tells us that by the Hopkins thiophene test he found no lactic acid in these urines, which were highly acid and did not decompose for many days, and certainly if any was present the amount was too minute to explain the high acidity or the failure of the urine to decompose. This result is

of interest, for Jerusalem, by his method, found a small quantity of lactic acid in the urine of a patient with pulmonary tuberculosis. As far as we have been able to investigate the matter we are therefore quite in the dark as to the cause of this peculiar high acidity of the urine that we are describing. Apparently tuberculous disease of pulmonary tissue leads to the formation of an unknown body or bodies which keep the urine highly acid, retard its decomposition, sometimes for over a hundred days, and, as we shall show presently, retard the formation of ammonia.

The obvious thought comes to one's mind that the failure to decompose is dependent upon the high acidity, and perhaps this is so to some extent. For example, three specimens from Case IV decomposed in two, three, and two days respectively, and in all the acidity was only between 2 and 3; these urines decomposed more quickly than any from the other patients suffering from tuberculous disease of the lungs, and they had the lowest acidity. But there is no direct constant ratio between the acidity and the rate of decomposition. For example, in Case I a specimen, the acidity of which was 5·6, decomposed in sixteen days; and one, the acidity of which was 5·5, was still acid at the end of a hundred and fifteen days. In Case II there is some association between the failure to decompose and the acidity, but it is very irregular; thus a urine with an acidity of 7·2 went alkaline in twenty-five days, and one with an acidity very little higher, viz. 8·4, was still acid at the end of a hundred and thirty-five days. In Case III it happened that three specimens had an acidity of 9·9; two went alkaline in twenty days and fifteen days respectively, but the third was still acid at the end of a hundred and eight days, and a specimen with an alkalinity of 10·2 turned acid in nineteen days. In Case V the specimen with the very high acidity of 30 turned alkaline in five days, but a specimen with an acidity of 8·3 remained acid eight days. Case VII had the high acidity of 11 and was still acid at the end of fifty days; but again the attempt to establish any direct relationship is frustrated in Case VIII, for the acidity of the two specimens was virtually identical, yet one turned alkaline in twelve days, the other was still acid at the end of twenty-seven. But this discrepancy between the acidity of the urine and the time during which it remains acid is equally striking in the urines which were obtained from patients suffering from other diseases than tuberculous disease of the lungs. For example, in one case of tuberculous peritonitis the urine with the highest acidity remained acid longest, and in the other the urine with the lowest acidity remained acid longest, in the first case of lobar pneumonia the urine with the highest acidity remained acid longest, and in the second case that with lower acidity remained acid longest. Another way of showing the want of relationship between the acidity and the time during which the urine remains acid is to contrast the second and third cases in Table I. If in both we disregard the one specimen which was still acid when this paper was written, we find that the average acidity in Case II was 6·48, that in Case III 9·31, yet on the average the urine remained acid 20·4 days in Case II and only eighteen days in Case III,

although in this the acidity was much greater. Therefore we learn that while the urine of patients with tuberculous disease of the lungs is often excessively acid and remains acid an unusually long while, yet no direct relationship can be traced between the excess of acid and the duration of the acidity.

We have in the table below compared the specific gravity with the number of days the urine remained acid in the eight cases of pulmonary tuberculosis (twenty-nine specimens).

| *Sp. gr.* | *No. of Specimens.* | *Days each specimen remained acid.* |
|---|---|---|
| 1·006 | 1 | Still acid at end of 108. |
| 1·007 | 2 | Still acid at end of 115, 12. |
| 1·008 | 5 | 28, 15, 10, 2, 2. |
| 1·009 | 2 | 25, 10. |
| 1·010 | 4 | 27, 19, 16, 3. |
| 1·011 | 2 | 20, 20. |
| 1·012 | 2 | 20, 17. |
| 1·014 | 3 | Still acid at end of 50, 16, 15. |
| 1·015 | 2 | Still acid at end of 135, 15. |
| 1·016 | 1 | 12. |
| 1·018 | 2 | Still acid at end of 27, 17. |
| 1·023 | 1 | 8. |
| 1·025 | 1 | 8. |
| 1·040 | 1 | 5. |

We see that the specific gravity of the urine in these cases was unusually low, and it is worthy of note that in Case IV, in which the specific gravity was 1·008, 1·010, and 1·008 in the three specimens, the acidity was very low, viz. 2·5, 2·6, and 2·9, and these three specimens decomposed in two, three, and two days respectively, so it may be that the prolonged acidity of the urine from some patients affected with tuberculous disease of the lungs is dependent in some degree on a high acidity associated with a low specific gravity; but there is no direct relationship between the specific gravity and the duration of acidity, for one specimen with a specific gravity of 1·006 was still acid at the end of a hundred and eight days, and one with a specific gravity of 1·015 was still acid at the end of a hundred and thirty-five days. On the other hand, two specimens with a specific gravity of 1·008 decomposed in two days, and one with a specific gravity of 1·040 turned alkaline in five days.

In the three first cases in Table I the acidity was estimated, not only when the urine was fresh, but again at the end of two days, at the end of seven days, and at the end of fourteen days. Reference to the table shows that invariably the acidity slowly fell, but the rate of fall was not the same in all the cases. In Case II a specimen which had an acidity as high as 5·2 at the end of fourteen days was still acid at the end of a hundred and thirty-five days, and in Case III one that had an acidity of 5 at the end of fourteen days was still acid at the end of a hundred and eight days; further, a specimen from Case III which had an

acidity of 5 at the end of fourteen days remained acid twenty-eight days. These figures appear to show that if at the end of a fortnight the acidity is still high the urine will remain acid a long while, but that the converse statement is not correct is shown by the fact that specimen 3 from Case I only had an acidity of 0·7 at the end of fourteen days, yet after a hundred and fifteen days it was still acid, and specimen 1 from Case II at the end of fourteen days had an acidity of 2·0 and remained acid twenty-five days, although specimen 3 from Case III, having at the end of the same time an acidity of 4·9, only remained acid fifteen days.

The fact that the urines from patients suffering from tuberculous disease of the lungs may remain acid for so long naturally led us to investigate the rate of growth of bacteria in them. The urines of Cases II and III were examined from this point of view. Each patient was carefully searched to make sure that no disease of the genito-urinary apparatus existed, and catheter specimens were taken with full precautions against infection of the urine from without. Specimens of the urine incubated at 37° C. for three days remained sterile. A tube containing 5 c.c. of the urine to be examined was taken and also one containing 5 c.c. of sterile broth. Each was inoculated with a loopful of a young twenty-hours culture in broth of the bacillus coli communis. Next, gelatine tubes were inoculated with a loopful of the broth and urine respectively and then plated out on gelatine at the end of five minutes, fifteen minutes, thirty minutes, one hour, two hours, and six hours respectively from the inoculation of the broth and urine by the bacillus coli communis. The gelatine plates were kept at the room temperature for a week and the number of colonies on each were then counted. The results are shown in Table II, and it will be seen that invariably there were fewer colonies of growth on the plates planted with the bacillus coli communis from the urine than in the plates planted from the broth; in other words, the urine from patients with pulmonary tuberculosis has considerable bactericidal power. To take examples at random. In experiment 1, at the end of thirty minutes there were 124 colonies surviving from the broth inoculation, and only 58 from the urine inoculation. In experiment 2, at the end of six hours there were 130 colonies surviving from the broth inoculation, and only 60 from the urine inoculation. In experiment 3 the respective numbers at the end of six hours were 40 and 12, and in experiment 4 at the end of five minutes 144 and 54. The observations upon the bactericidal properties of these urines are supported by the observation made in 1892 that the urine of patients with pulmonary tuberculosis contained very few bacilli, even after a considerable time. Yeast-like organisms, however, grow freely in such urine and moulds grow on it, and when the urine has remained acid over a month there is often a considerable mass of moulds on its surface. That the growth of the moulds is the cause of the acidity is very unlikely, for moulds also grow on those that turned alkaline, and there was no sugar in any of these urines from which the moulds could produce acid.

In the paper published in 1892 it was pointed out that these urines which remain acid a very long while gradually develop a disagreeable smell like rotten cheese. That was also true of the specimens now being described; but in 1892

several of the specimens which remained acid a long while gradually became dark until, after some months, they were black. But not all underwent this change, for it was only seen in 19 specimens out of 182; so it may be a mere accident that it has not been observed this time, or it may be that it was due to some micro-organism which chanced to be present in the air in 1892, but which was not present in 1909. It would be interesting to know whether but few patients with tuberculosis of the lungs suffer from genito-urinary tuberculosis, for perhaps the bactericidal properties of the urine prevent the onset of genito-urinary tuberculosis. Not many cases of tuberculosis do better with tuberculin treatment than those of the genito-urinary tract; perhaps this is in some way connected with the peculiarities of the urine.

The urines from Cases II and III were examined to see if they contained any opsonins for bacillus coli communis or bacillus tuberculosis. The examination was made in the usual way, but instead of normal serum, urine from a healthy person was used, and instead of the serum to be examined for its opsonic index the urine from one of these cases was substituted. In neither the healthy urine nor the urine from the patients with tuberculous disease of the lungs could any opsonins for either the bacillus coli communis or the bacillus tuberculosis be demonstrated. These urines were examined for phenol and indol, but none was found, so that the tardiness of their decomposition cannot have been due to either of these bodies. Abundance of indican was often present; this was probably owing to increased intestinal decomposition. The specimen from Case II, which was still acid at the end of a hundred and thirty-five days, was examined for ammonia a hundred days after it was passed. It was found to contain 1·407 grms. per litre, the normal in fresh urine being 0·46, which indicates that the acidity is really greater than appears, and also that as the amount of ammonia is so small a large amount of urea is still undecomposed. We have carefully examined the clinical facts noticed about all the patients suffering from pulmonary tuberculosis whose urine has been used for these observations, and we can detect nothing unusual about them. Case IV, in which the acidity of the urine was so low and in which this fluid decomposed so much more rapidly than in the other cases, was the only one with an ischio-rectal abscess. Likewise in the series published in 1892 no association between the state of the urine and any particular symptom could be discovered, but all the cases in that series and in this now published were sufficiently ill to be in the hospital. In every case used for the present paper, tubercle bacilli were found in the expectoration, and abundant physical signs were present in the lungs. In no case was any drug used.

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## TABLE I

The Acidity is expressed as the number of cubic centimetres of decinormal soda solution necessary to neutralize 20 c.c. of urine.

| PATIENT. | DIAGNOSIS. | SPEC. No. | ACIDITY FRESH. | ACIDITY 2 DAYS. | ACIDITY 1 WEEK. | ACIDITY 2 WEEKS. | HOW LONG REMAINED ACID. | SP. GR. |
|---|---|---|---|---|---|---|---|---|
| *Case I* | Phthisis | 1 | 4·5 | 3 | 1 | | 10 days | 1·008 |
| ,, | ,, | 2 | 5·6 | 4·9 | 2·2 | 1·1 | 16 days | 1·010 |
| ,, | ,, | 3 | 5·5 | 4·1 | 2·3 | 0·7 | Still acid at end of 115 days | 1·007 |
| *Case II* | Phthisis | 1 | 7·2 | 7·2 | 6·5 | 2·0 | 25 days | 1·009 |
| ,, | ,, | 2 | 6·4 | 6·2 | 5·8 | 3·2 | 20 days | 1·011 |
| ,, | ,, | 3 | 6·2 | 6·0 | 5·0 | 2·2 | 20 days | 1·011 |
| ,, | ,, | 4 | 6·4 | 6·2 | 6·0 | 4·1 | 27 days | 1·010 |
| ,, | ,, | 5 | 8·4 | 8·2 | 8·0 | 5·2 | Still acid at end of 135 days | 1·015 |
| ,, | ,, | 6 | 6·2 | 6·0 | 4·8 | 2·2 | 10 days | 1·009 |
| *Case III* | Phthisis | 1 | 9·9 | 9·7 | 6·2 | 3·1 | 20 days | 1·012 |
| ,, | ,, | 2 | 10·2 | 10 | 9 | 4·1 | 19 days | 1·010 |
| ,, | ,, | 3 | 9·9 | 9·2 | 8·1 | 4·9 | 15 days | 1·008 |
| ,, | ,, | 4 | 10 | 8·5 | 7·9 | 5 | 28 days | 1·008 |
| ,, | ,, | 5 | 8 | | | 2·2 | 12 days | 1·007 |
| ,, | ,, | 6 | 8·2 | 6·6 | 4·3 | 2·1 | 15 days | 1·014 |
| ,, | ,, | 7 | 9 | | | 4 | 17 days | 1·012 |
| ,, | ,, | 8 | 9·9 | 8·7 | | 5 | Still acid at end of 108 days | 1·006 |
| *Case IV* | Phthisis | 1 | 2·5 | | | | 2 days | 1·008 |
| ,, | ,, | 2 | 2·6 | | | | 3 days | 1·010 |
| ,, | ,, | 3 | 2·9 | | | | 2 days | 1·008 |
| *Case V* | Phthisis | 1 | 30 | | | | 5 days | 1·040 |
| ,, | ,, | 2 | 8·3 | | | | 8 days | 1·025 |
| ,, | ,, | 3 | 6·9 | | | | 8 days | 1·023 |
| *Case VI* | Phthisis | 1 | 6·4 | | | | 15 days | 1·015 |
| ,, | ,, | 2 | 5·9 | | | | 16 days | 1·014 |
| ,, | ,, | 3 | 6·4 | | | | 17 days | 1·018 |
| *Case VII* | Phthisis | 1 | 11 | | | | Still acid at end of 50 days | 1·014 |
| *Case VIII* | Phthisis | 1 | 8·8 | | | | 12 days | 1·016 |
| ,, | ,, | 2 | 9 | | | | Still acid at end of 27 days | 1·018 |
| *Case IX* | Tub. Perit. | 1 | 2·2 | | | | 2 days | 1·012 |
| ,, | ,, | 2 | 4 | | | | 4 days | 1·010 |
| ,, | ,, | 3 | 3·9 | | | | 2 days | 1·012 |
| *Case X* | Tub. Perit. | 1 | 3·2 | | | | 4 days | 1·009 |
| ,, | ,, | 2 | 4·3 | | | | 1 day | 1·015 |
| ,, | ,, | 3 | 5·0 | | | | 2 days | 1·010 |
| *Case XI* | Addison's Disease | 1 | 4 | | | | 3 days | 1·010 |
| ,, | ,, | 2 | 4·9 | | | | 2 days | 1·012 |
| ,, | ,, | 3 | 4·2 | | | | 4 days | 1·010 |

TABLE I (*continued*)

| PATIENT. | DIAGNOSIS. | SPEC. NO. | ACIDITY FRESH. | ACIDITY 2 DAYS. | ACIDITY 1 WEEK | ACIDITY 2 WEEKS | HOW LONG REMAINED ACID. | SP. GR. |
|---|---|---|---|---|---|---|---|---|
| *Case XII* | Staphyl. Septic. | 1 | 5·9 | | | | 5 days | 1·011 |
| ,, | ,, | 2 | 6·2 | | | | 4 days | 1·013 |
| ,, | ,, | 3 | 5·4 | | | | 3 days | 1·013 |
| *Case XIII* | Acute Lobar Pneum. | 1 | 6·9 | | | | 2 days | 1·025 |
| ,, | ,, | 2 | 7·2 | | | | 4 days | 1·022 |
| ,, | ,, | 3 | 6·0 | | | | 3 days | 1·020 |
| *Case XIV* | Acute Lobar Pneum. | 1 | 4·7 | | | | 2 days | 1·015 |
| ,, | ,, | 2 | 4·5 | | | | 4 days | 1·013 |
| *Case XV* | Lobar Pneum. | 1 | 4·2 | | | | 3 days | 1·014 |
| *Case XVI* | Lobar Pneum. | 1 | 4·8 | | | | 2 days | 1·014 |

TABLE II

EXPERIMENTS ON THE BACTERICIDAL PROPERTIES OF URINES FROM PATIENTS WITH PULMONARY TUBERCULOSIS

| PATIENT. | EXPT. NO. | TIME BETWEEN INOCULATION AND PLATING. | NO. OF COLONIES SURVIVING IN BROTH. | NO. OF COLONIES SURVIVING IN URINE. |
|---|---|---|---|---|
| *Case II* | 1 | 5 minutes | 52 | 44 |
| ,, | 1 | 15 minutes | 93 | 62 |
| ,, | 1 | 30 minutes | 124 | 58 |
| ,, | 1 | 1 hour | 120 | 52 |
| ,, | 1 | 2 hours | 54 | 15 |
| ,, | 1 | 6 hours | 44 | 10 |
| *Case II* | 2 | 5 minutes | 110 | 60 |
| ,, | 2 | 15 minutes | 115 | 64 |
| ,, | 2 | 30 minutes | 130 | 54 |
| ,, | 2 | 1 hour | 140 | 69 |
| ,, | 2 | 2 hours | 148 | 72 |
| ,, | 2 | 6 hours | 130 | 60 |
| *Case III* | 3 | 5 minutes | 140 | 50 |
| ,, | 3 | 15 minutes | 150 | 59 |
| ,, | 3 | 30 minutes | 100 | 40 |
| ,, | 3 | 1 hour | 66 | 30 |
| ,, | 3 | 2 hours | 58 | 22 |
| ,, | 3 | 6 hours | 40 | 12 |
| *Case III* | 4 | 5 minutes | 144 | 54 |
| ,, | 4 | 15 minutes | 140 | 58 |
| ,, | 4 | 30 minutes | 90 | 42 |
| ,, | 4 | 1 hour | 100 | 46 |
| ,, | 4 | 2 hours | 54 | 20 |
| ,, | 4 | 6 hours | 44 | 25 |

# PERIPHERAL BIRTH PALSY

By E. F. TREVELYAN

With Plates 22–24

Paralysis in the infant due to injuries sustained during the process of birth may be central or peripheral in character. The peripheral form may affect the face, arm, and quite exceptionally even the leg. Facial birth palsy is usually of a purely temporary character, whereas the changes in the brachial plexus causing the paralysis of the arm are more lasting, and therefore the paralysis more permanent.

The lesions found in the brachial plexus, either after death or at the time of operation in the few cases at present available, mostly involve the fifth, sixth, and even the seventh cervical nerves, or more rarely the eighth cervical and first dorsal. They consist in haemorrhage in and about the nerves and also stretching and tearing of the nerves themselves, which may lead to partial or complete rupture of the axis cylinders. A total rupture of a nerve trunk most often affects the fifth cervical, but at present it is impossible to say how frequent this total rupture is. Bullard saw one trunk actually ruptured and several others lacerated. Even more than one nerve may be severed. In Carmalt's case the fifth and sixth cervical nerves were torn out of the spinal cord. Beyond these primary changes, secondary effects may occur, as is well pointed out by Prout. The haemorrhages which take place in the sheaths of the damaged nerves, or the cicatricial tissue which ultimately develops, may press on the nerve fibrils, interfering with repair and leading to permanent paralysis. Changes may also take place outside the nerves, and adhesions may form between the nerves and the cervical fascia, which may itself be thickened. Thus in one of my cases (No. 4), upon which Mr. Walter Thompson recently operated in the Leeds Infirmary, the upper nerves of the brachial plexus appeared to be embedded in the much-thickened cervical fascia, and the sheaths of the nerves themselves were also greatly thickened. In this case the paralysis of the whole arm was complete (Fig. 2). A bulbous enlargement may form on the end of a divided nerve or a cicatricial thickening develop in the course of the lacerated nerve trunk. In Eversmann's case no nerve fibres could be traced through such a cicatricial thickening. Some nerve fibres may, however, alone be damaged while others remain intact, as was recently demonstrated in Barlow and Ballance's case. Thus, by stimulation of the fifth cervical nerve above the

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enlargement, these authors found that whereas the deltoid and other muscles failed to contract, the spinati responded. Exceptionally, a fracture of the clavicle or a separation of the epiphysis may occur and pressure be thus exercised on the plexus.

The exact mechanism by which brachial birth palsy is produced has only been satisfactorily demonstrated of recent years. Up to the time of the experiments by Fieux, compression of the brachial plexus by the forceps, by the finger, or even by the clavicle was the prevailing view. Fieux, however, proved that in the foetus the nerves of the brachial plexus could easily be made taut and eventually ruptured by separating the head from the shoulders. These experiments were repeated and extended by Schoemaker, who showed that a separation of the head from the shoulder, even through an angle of 30° laterally from the middle line, was sufficient to bring about these results. This author, on the other hand, also states that this separation of the head from the shoulder is not the exclusive cause of birth palsy, and the occurrence of facial birth palsy after the use of the forceps proves that pressure can at any rate cause paralysis. More recently the whole subject has been newly investigated by Taylor, Prout, and Clark, and the importance of stretching and laceration as an etiological factor has been further emphasized.

The importance of the exact study of how the paralysis is produced is obvious, and Schoemaker has even formulated prophylactic rules based on his experimental investigations.

It is clearly a fact that birth palsy is more frequent the more difficult and prolonged the labour, and although it may exceptionally occur in a spontaneous delivery, it is incomparably more frequent when artificial help has to be given. This artificial help includes all manipulations as well as the application of the forceps.

*Distribution of the Paralysis.* Facial palsy is usually admitted to be the most frequent form of birth palsy. It involves of course the whole of the facial nerve.

The paralysis of the arm accords precisely with the paralysis which may occur as the result of an injury to the brachial plexus. The upper part of the plexus, viz. the fifth, sixth, and even the seventh cervical nerve, may be solely involved, and the paralysis be of the typical Duchenne-Erb type, or the lower part of the plexus alone may be implicated, producing a paralysis of the Klumpke-Déjerine variety. At times the whole plexus may be affected and the arm be completely paralysed. Mixed types of plexus paralysis have also been described.

*Paralysis of the Upper-arm type.* This is by far the most common form of brachial birth palsy. It is generally due to a lesion of the fifth cervical nerve or of the junction of the fifth and sixth. The following muscles are usually involved: the deltoid, biceps, coraco-brachialis, brachialis anticus, and brachio-radialis, as well as the supra- and infraspinatus and teres minor and the supinator brevis. Wilfrid Harris holds that section of fifth cervical alone will

produce this form of paralysis, and in this he is followed by Sherran. The latter says that co-involvement of sixth cervical only adds at most paralysis of the clavicular portion of the pectoralis major. The radial extensors of the wrist are stated by Harris to be innervated by the fifth cervical, and in at least one of my cases these radial extensors have been involved (Case 6 and probably Case 9). The triceps (seventh cervical) may also be affected (Case 9).

In paralysis of this type, the early attitude of the limb is characteristic. The arm is held extended closely apposed to the body and strongly pronated, so that the ulnar border may even look forward (Fig. 1 ; Case 4). In such a case the child may be quite unable to carry out any movements at the shoulder, or to flex the forearm on the arm, or to supinate the hand. The remaining movements of the forearm and hand are unaffected. The wasting of the muscles may be obvious unless the child is plump, when it cannot so easily be made out, only a flabbiness of the muscles being present and sometimes not even that.

Later the attitude of the limb undergoes some slight alteration. The pronated position still persists, but the arm is held slightly abducted from the trunk and there is some flexion present at the elbow (Fig. 3). It is interesting to note how rarely any considerable dropping of the head of the humerus is seen as a result of birth palsy, whereas this deformity is a striking feature of infantile paralysis of the upper-arm type. It is, however, present in moderate degree in one of my cases (No. 11).

The *residual* paralysis varies greatly in degree, but in every case which I have observed over sufficiently long periods of time, it has never been wholly absent. The two movements most often defective are (1) external rotation of the humerus with supination of the forearm and (2) elevation of the arm above the level of the shoulder. Whereas the explanation of the former is comparatively easy, viz. the persistent paralysis of the external rotators of the humerus due to injury to the suprascapular nerve, the same cannot be said of the inability to raise the arm above a right angle. In none of my cases has there been any evidence of paralysis of the serratus magnus muscle. Thus when the arm has been either actively or passively advanced there has been no winging of the scapula. The innervation of the serratus magnus would not lead one to expect that this muscle would be involved. Again, there has been no reason to assume any impaired function in the lower part of the trapezius, which latter is known to assist in fixing the scapula in the elevation of the arm above the level of the shoulder. Some have sought the explanation in an alteration in the position of the head of the humerus, viz. a partial backward dislocation such as is easily demonstrated to be present in Case 13. The defective development of the whole shoulder girdle is well seen in this case (Figs. 4 and 5). The slight flexion at the elbow referred to above must also interfere with the complete elevation of the arm, for in the healthy individual this same movement cannot be thoroughly carried out if the forearm is held flexed on the upper arm. The slight flexion at the elbow in the later stages of birth palsy has itself been attributed to a dis-

placement of the head of the radius. Quite exceptionally paralysis of the upper-arm type may be bilateral in character as in Case 3.

Paralysis of the lower-arm type is much less common than that of the upper-arm type. I have only two pure cases of it in my list (Cases 19 and 22), and these I only saw on one occasion, as I have quite failed to trace them. Many cases so described have been the remains of total paralysis of the arm, as has been pointed out by Thomas.

Sometimes the whole brachial plexus is involved and then the arm may hang flaccid and motionless. There are four or five such cases in my series, but I have only observed two of these cases (Nos. 4 and 7) for any long period of time. The other cases (Nos. 16, 20, and possibly 18) have only been seen on one occasion. There are two examples of bilateral birth palsy among these five cases (Nos. 4 and 16). One of these cases (No. 16) I saw recently with Dr. Fawcett of Leeds, and he has since informed me that the child is beginning to improve. The other (No. 4) is the case in which an operation has been performed on the totally paralysed right arm.

In the mixed form of brachial birth palsy the paralysis does not fall into any well defined type. I have classed Case 6 under this heading. No doubt most of such cases may be explained by an anomalous residual paralysis after total plexus palsy.

I have only seen one case of paralysis of the leg which I thought was due to injury sustained during birth. The child is one of twins and was born first with the head presenting. The paralysis noticed at once after birth is flaccid in character and involves uniformly the whole of the limb. The child is now thirteen months old and shows no signs of improvement. The case is not a clear one, but it is certainly quite unlike infantile paralysis.

Contractures and deformities may occur in birth palsies. They are more common in the forearm and hand. In Case 7 there is a well-marked claw hand (Fig. 6) and in Case 6 a curious ulnar flexion (Fig. 7).

All the various degrees of residual paralysis are to be seen in my series of cases, from almost complete recovery, as in Case 8, up to an almost useless limb (Case 4). The residual paralysis is usually more extensive in the lower-arm type. Short details as to the extent of the recovery in my cases will be given when the prognosis is discussed.

*Diagnosis.* As a rule there is no difficulty in recognizing brachial birth palsies. Injuries (and possibly disease) about the shoulder must of course be excluded, by skiagram if necessary. Some of the injuries, such as fracture of the clavicle, &c., might possibly cause the paralysis, but not at all necessarily. In Eversmann's case there was a fracture of the clavicle on one side and a brachial palsy on the other. Cerebral birth palsies are easily differentiated. Infantile paralysis of the upper- and lower-arm types may closely resemble birth palsies. Thus, in a boy aged twelve whom I recently saw with infantile paralysis affecting the whole of both arms, there was a considerable residual palsy in each arm, not at all unlike that seen after birth palsy. In two of a series of fifty cases

(Nos. 18 and 41) of infantile paralysis which I recorded a short time ago, the distribution of the paralysis resembled that found in birth palsy of the lower-arm type. It should be remembered that infantile paralysis is almost unknown during the first six months of life, thus showing an important distinction from birth palsy.

In the case of supposed facial birth palsy (No. 24) which has persisted, the differential diagnosis from congenital facial palsy has to be considered. Of course it is improbable that a congenital defect should limit itself alone to the facial nerve or its nucleus.

In regard to the diagnosis of birth palsy of the leg, I have nothing further to add to what has already been said under the description of a supposed case (No. 23).

The diagnosis should not be limited to the mere labelling of the disease or to the naming of the type of the brachial palsy. The attitude of the limb should be observed and every movement carefully examined, the result being noted for future comparison. This may be by no means an easy task in the young infant, but with patience it can generally be carried out. In the older child the best method is to impose a certain movement on the sound limb and to get the child to imitate it with the affected limb. A sufficient knowledge of the action of the muscles in carrying out movements is of course essential. Such a book as that by the late Dr. C. E. Beevor on Muscular Movements may be very useful in this respect.

Before discussing the details of prognosis, I will briefly outline the improvement which has occurred in my cases, some of which have been under my observation for many years.

Albert B. (Case 8). Here the recovery is almost complete. There is still some weakness in supination, otherwise all movements can satisfactorily be carried out in this arm.

Ethel M. (Case 14). All movements are possible except supination of the hand and external rotation at the shoulder. The arm can be elevated above the shoulder.

Mary S. (Case 3) has, I believe, made as complete recovery as is likely to be seen in a severe birth palsy, here bilateral. All movements are possible and the arms can be raised above the shoulder. External rotation and supination are defective.

Elsie N. (Case 10) can use her arm in every direction, but she cannot raise it above a right angle.

Thomas W. (Case 13) has made a good recovery. He can raise his arm slightly above a right angle, but he cannot rotate it externally. He can supinate the hand to mid-position.

Horace Sm. (Case 2) promises to make a good recovery.

Cecil B. (Case 11) has a useful arm, notwithstanding the dropping of the humerus and the considerable atrophy of the deltoid.

Arthur H. (Case 5) will have a useful arm. All movements are possible in it except complete supination and carrying the arm above a right angle.

John D. (Case 15) has made a very fair recovery. He cannot raise the arm above the shoulder nor yet rotate it externally. Flexion and extension at the elbow-joint are only fairly good.

George C. (Case 9). The arm has made a very incomplete recovery. No supination is possible. The deltoid and the flexors of the forearm act feebly. The triceps and radial extensors also seem weak.

Dorothy B. (Case 12). Recovery is far from satisfactory. The forearm can be supinated to mid-position. External rotation at the shoulder is impossible and the arm cannot be carried upwards above a right angle. There is a considerable flexion of the forearm on the arm, so that the usefulness of the limb is much impaired.

The recovery in the case of Elsie A. (Case 6) and Ernest H. (Case 7) has been considerably impaired by the contractures which have occurred. Perhaps a more careful treatment might have prevented these deformities and have allowed the weakened antagonists to recover. An operation is proposed in Case 6.

Arthur St. (Case 4) shows complete paralysis of the whole of the right arm. Some improvement has certainly taken place in the left arm, and this is now increasing in hospital. The right arm has been operated on as stated above.

Frank C. (Case 1) promises to make a very good recovery.

There is as yet no improvement in the leg in Case 23 and the paralysis of the face in Case 24 is permanent. The remaining cases were only seen once or twice and could not be further traced.

*Prognosis.* Thus, although there is not a single case of complete recovery in my series of cases of brachial birth palsy, there are at least two, viz. Nos. 8 and 10, which come very near it.

All are agreed as to the almost invariably favourable prognosis of facial birth palsy. Recovery occurs in from one to four weeks. Very rarely indeed the palsy may persist, as in the case mentioned above.

The favourable issue of this form of birth palsy is no doubt largely due to the slight degree of the injury (viz. compression of the facial nerve). In brachial birth palsy, however, the severity of the injury is almost invariably greater, and another factor also comes into play here as this severe injury acts at a considerable distance from the peripheral distribution of the nerves. Bruns, in a well known paper, pointed out that the prognosis of paralysis due to injuries of the brachial plexus was not nearly as good as that of injuries to the peripheral nerves (in his cases 26 per cent. of recoveries in the former as against 66 per cent. in the latter). He is inclined to think that the unfavourable prognosis may be partly due to coincident injury to the spinal cord. No doubt injuries to the cord have been proved in isolated cases of brachial birth palsy (Phillippe and Cestan, Raymond, Carmalt, and others), yet it is doubtful whether the explanation can be widely applied. Sherren objects to Bruns' conclusions, but most will agree with these conclusions as far as they apply to the prognosis of peripheral as against plexus nerve injuries.

However this may be, the prognosis of birth palsy must largely turn on the severity of the lesion. If the lesion involves an actual tearing through

of a nerve or nerves of the plexus, then the prognosis must be hopeless unless the ends of the nerves can be brought together. Or again, if secondary changes occur in or about the nerves as mentioned above, recovery may be considerably interfered with. Unfortunately there is no absolute criterion as to a rupture of the nerve in the plexus in these cases.

The following factors may assist in the estimation of the severity of the lesion (including rupture):—

1. The electrical reactions. If a rupture of a nerve is present, no stimulation of the nerve above the rupture can call forth response. In young infants, however, the electric examination is extremely difficult and must be carried out under anaesthesia. I had recently the opportunity of thus examining Case 4 just before the operation on the brachial plexus. All the muscles in the upper arm reacted to a faradic current of moderate intensity, but no reaction could be obtained in the intrinsic muscles of the hand to faradism or galvanism. The muscles of the upper arm responded to galvanism but showed polar changes. Therefore it is hoped that improvement will be obtained by the freeing of the nerves at the operation. The electrical examination is not, however, always entirely reliable even when carried out under anaesthesia.

2. Thickening over the region of the plexus about Erb's point does not, so far as I know, really indicate that more severe lesions have actually taken place in or about the nerves of the plexus. I have seen more favourable cases where a considerable mass could be felt there (Case 13) and less favourable cases where nothing has been made out on careful exploration of the supraclavicular fossa with the finger (Case 9).

3. The degree and extent of the paralysis may give some indication as to the severity of the lesion (Case 7).

4. Lapse of time must be an important element in the prognosis. It may obviously be a most difficult matter to give a prognosis in the early weeks after birth, and, on the other hand, the absence of any recovery throughout weeks and months makes it probable that the severity of the injury precludes a really favourable issue. The most difficult question is to fix this limit of time. It has been said by some that if there is no improvement in three months there will be none. Others name twelve months. My experience is decidedly in accord with the latter view. I have seen great improvement occur in the second and even the third year where there has been little satisfactory progress before (Case 3).

5. The amount of force used and the particular manipulation employed may also be an indication of the severity of the lesion. Thus most are agreed that the worst forms occur in breech presentations with the extension of one or both arms (Case 4). On the other hand, a mere compression is not likely to produce serious consequences even in the case of brachial birth palsy. Thus in Hochstetter's case, where the mark of the forceps was visible just above the clavicle on the affected side, the paralysis was incomplete and recovery began as early as the third or fourth day. In a similar case by Besse the patient was

practically well in a short time. Again, the chances of recovery are better, should the paralysis occur after a spontaneous birth, and especially if the presentation be a head one.

Whatever be the data available for coming to a conclusion, there can be no doubt that the views upon the prognosis of birth palsy are by no means in accord. Some are satisfied that the percentage of so-called spontaneous recoveries is as high as 70 per cent. and even more, whereas on the other hand Thebonneau, Baudny, Weil, and others look upon the prognosis as grave and even very grave. Is there any way of reconciling these discordant views? It is conceivable that hospital physicians might see rather a different class of case than do those engaged in obstetric practice. The latter would meet with the slighter cases which the former might never see. Thus the question arises whether there is a group of mild cases of brachial birth palsy which terminate in recovery in a few weeks' time. Facial palsy is known to recover in this way, but then, as I have endeavoured to point out, the causation is very different in point of view of severity. Some cases of mild brachial birth palsy have undoubtedly been recorded, as by Hochstetter (see above). Comby also speaks of such a class of case, and records one of his own in which recovery took place in fourteen days. The question could easily be settled by the systematic noting of all cases of rapidly recovering brachial birth palsy. My own surmise is that such cases would be few and far between. My series contains several cases seen within a few weeks or even days of birth, and the subsequent progress of these cases has not been different from those seen at a latter date.

My experience, small though no doubt it is, agrees with those who take a serious view of brachial birth palsy. Unless in the mildest of cases, there can in my opinion hardly be a complete recovery, so that the question resolves itself into whether there will be a useful limb or not. The nearest approach to recovery among my cases is Case 8. The majority of them have, however, a useful arm, but in several the results are quite unsatisfactory. The above view would also take into account the result of operative treatment, and, as this latter can only convert a useless or nearly useless limb into a more or less useful one—a no small benefit to the individual as everybody will admit (see cases by Kennedy, Taylor, Prout, and Clark, Barlow and Ballance, Osterhaus, and others)—operation should only be undertaken on this understanding.

The question of prophylaxis is obviously of great importance, but it does not come within my actual experience. The main point appears to consist in the avoidance of any manipulation, either in traction or other, which would unduly separate the head from the shoulders and so put the plexus on the stretch.

*Treatment.* I shall only refer briefly to the principles underlying the management of these cases. (1) Paralysed muscles must on no account be allowed to remain overstretched. Therefore the arm should be carried in a sling. (2) The nutrition must be maintained, and this is best done by systematic rubbing and passive movements. Electrical treatment is not often

of value, as it frightens the infant. By far the most important of all in my view is (3) the cultivating of every voluntary movement, even the slightest, in the paralysed muscles. This is not easy in the infant, but the mother of Case 3 has indefatigably carried it out by means of coins, &c., held in a position for the child to grasp at, and I believe much benefit has been thus obtained. This is a principle of the treatment of all forms of paralysis, whether in the child or adult, as soon as the active causes of the disease have ceased to operate, and my experience is that it does not always receive the attention it deserves. In Case 8, where the recovery is almost complete, all movements being easily effected, the child does not use the arm nearly as much as it should do. This tendency not to use the less-developed limb must be steadily counteracted. In older children systematized exercise or even a Sandow developer may be of value. The above-named measures will be ineffective if the nerves are ruptured or virtually ruptured, and there is then only one treatment, and that is suture. Even if the rupture were certain it is doubtful whether it would be wise to operate in very early infancy, owing to the danger of shock and the small size of the parts concerned. But, as has been mentioned above, it is almost impossible to say definitely that the nerve trunk is ruptured, and improvement may occur later where rupture has been suspected. Absolute paralysis even for months does not mean rupture (Case 4). Thus it becomes a very difficult matter to determine the early limit of time for intervention. Some mention three months (Thorburn, Kennedy, and Sherran), but I should decidedly follow the suggestion of Clark and others, and make it twelve months or thereabouts. In a recent contribution to the subject Osterhaus adopts the latter date. If the near limit of time is not easily fixed, the same difficulty applies to the far limit, for a time comes when the intervention may be useless, that is, if the muscles become so altered as to be unable to develop. Perhaps the electric reactions would give some indication as to the far limit, but the subject is one of much difficulty and little can be definitely stated until more experience is forthcoming.

Finally, the after-treatment must be most carefully carried out after suture. It may require long periods of time before improvement occurs.

## Peripheral Birth Palsy.

(*Twenty-four Cases.*)

| No. | Name | Age | Age when first seen | Arm | Type | Recovery | Birth |
|---|---|---|---|---|---|---|---|
| 1 | Frank C. . . . . | 21 months | 11 days | Right | Upper | Good | V. M. |
| 2 | Horace Sm. Fig. 2. . | 11 months | 10 weeks | Left | Upper | Good | V. F. |
| 3 | Mary S. . . . . | 22 months | 10 weeks | Both | Upper | Very good | Br. |
| 4 | Arthur St. Fig. 1 . . | 2 years | 5 weeks | Both | Whole | Bad | Br. |
| 5 | Arthur H. Fig. 8 . . | 3⅛ years | 3 years | Left | Upper | Good | D. |
| 6 | Elsie A. Fig. 7 . . . | 8 years | 15 months | Right | Mixed | Bad | M. |
| 7 | Ernest H. Fig. 6 . . | 7⅓ years | 6 months | Left | Whole | Bad | F. |
| 8 | Albert B. . . . . | 6½ years | 7 weeks | Right | Upper | Very good | V. F. |
| 9 | George C. Fig. 3 . . | 7½ years | 5 weeks | Left | Upper | Slight | Tr. |
| 10 | Elsie N. Fig. 11 . . | 8 years | 6 weeks | Right | Upper | Good | V. F. |
| 11 | Cecil B. Fig. 9 . . . | 8 years | 8 years | Right | Upper | Fairly good | D. |
| 12 | Dorothy B. Fig. 10 . | 12 years | 2 years | Left | Upper | Slight | Tr. |
| 13 | Thomas W. Figs. 4 & 5 | 14 years | 5 weeks | Left | Upper | Good | D. |
| 14 | Ethel M. . . . . | 15 months | 2½ months | Left | Upper | Good | N. |
| 15 | John D. . . . . | 14 years | 13 years | Left | Upper | Fairly good | F. |
| 16 | Vincent L. Fig. 12 . . | 9 weeks | 10 weeks | Both | Whole | Improving | V. |
| 17 | Wm. H. B. . . . . | 3½ months | 12 weeks | — | Upper | — | Br. |
| 18 | Thomas E. . . . . | 6 weeks | 6 weeks | — | ? Whole | — | F. |
| 19 | Leonard P. . . . . | 1 year | 1 year | Left | Lower | — | D. |
| 20 | John C. . . . . | 15 months | 15 months | — | Whole | — | F. |
| 21 | A. S. M. . . . . | 6 months | 6 months | Left | Upper | — | F. |
| 22 | Joseph C. . . . . | 2 years | 2 years | Left | Lower | — | Br. |
| 23 | Grace C. . . . . | 13 months | 11 months | Leg Right | Whole | None | N. |
| 24 | John McN. . . . . | 4 years | 4 years | Face Right | Total | None | D. |

Br. = Breech. D = Difficult. F = Forceps. M = Manipulation. N = Normal.
Tr. = Transverse. V = Vertex.

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## DESCRIPTION OF PLATES.

FIG. 1. Case 4. Total Bilateral Birth Palsy. Right arm completely paralysed; has since been operated upon. Left arm is distinctly improved.

FIG. 2. Case 2. Birth Palsy of upper-arm type, showing characteristic attitude (early).

FIG. 3. Case 9. Birth Palsy of upper-arm type, showing later attitude. Recovery slight.

FIG. 4. Case 13 (front view). Birth Palsy of upper-arm type. Useful arm. Arm ill developed. Supination to mid-position possible.

FIG. 5. Case 13 (back view). Higher position of scapula, which is ill developed. Head of humerus is displaced backwards.

FIG. 6. Case 7. Birth Palsy of whole-arm type. Recovery bad. Claw. Brother to Case 5.

FIG. 7. Case 6. Birth Palsy of whole-arm type. Recovery bad. Deformity of hand.

FIG. 8. Case 5. Birth Palsy of upper-arm type. Recovery good. Brother to Case 7.

FIG. 9. Case 11. Birth Palsy of upper-arm type. Useful arm. Dropping of humerus. Brother to Case 12.

FIG. 10. Case 12. Birth Palsy of upper-arm type. Recovery very imperfect. Sister to Case 11.

FIG. 11. Case 10. Birth Palsy of upper-arm type. Good recovery, but arm is smaller and is not used as much as the sound one.

FIG. 12. Case 16. Total Bilateral Birth Palsy. Both arms show some improvement, but the left arm remains the worse of the two.

FIG. 1 (Case 4)

FIG. 2 (Case 2)

FIG. 3 (Case 9)

FIG. 4 (Case 13)

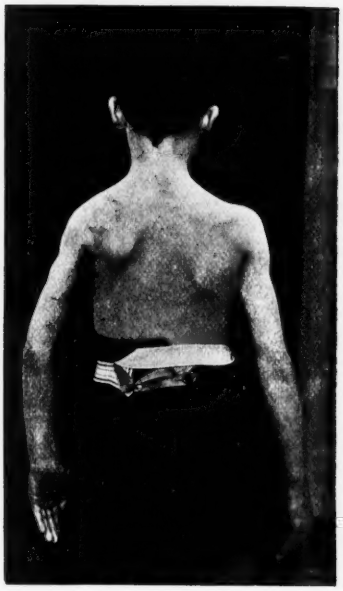


FIG. 5 (Case 13)

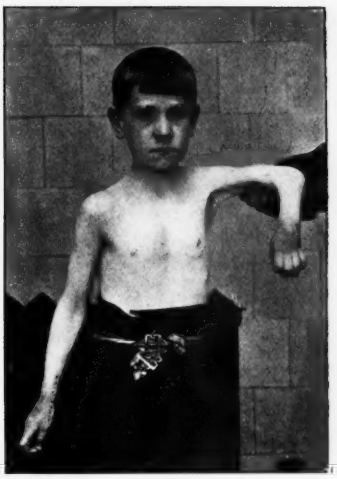


FIG. 6 (Case 7)

FIG. 7 (Case 6)

FIG. 8 (Case 5)

FIG. 9 (Case 11)

FIG. 10 (Case 12)

FIG. 11 (Case 10)

FIG. 12 (Case 16)

# CLINICAL OBSERVATIONS ON THE EFFECTS OF CERTAIN DRUGS IN DIABETES MELLITUS

By ARTHUR J. HALL

*Preliminary Remarks.*

THE primary object of these clinical observations was to ascertain the effects of opium, or its alkaloid codeia, on various symptoms in diabetes mellitus; in what respect, if any, the crude drug differed from the alkaloid in action; and whether such effects varied with the dose given.

In addition to these, secretin and aspirin were tried under similar conditions. For this purpose a series of nine cases of ordinary diabetes were placed, as far as possible, under similar conditions.

The patients under observation were in each case in-patients of medical wards under ordinary ward conditions. Each day a record was kept of (1) the total quantity of liquid consumed (exclusive of that taken in food and gravy, &c.), (2) the total quantity of urine excreted, (3) the percentage of sugar in a specimen of such mixed daily urine. In addition, the patient was weighed each week, and the usual daily record of temperature, pulse, respirations, and motions was kept.

In the carrying out of these observations care has been taken to avoid any gross errors, but it is important that the records should not be taken for more than they are actually worth, namely, a rough general comparison of clinical results. In order to reduce errors as much as possible the periods over which any particular variation of diet or treatment has been tried have been made of considerable length. Thus, in most cases, at least a week has been the minimum period, whilst two or three weeks, or even longer, have been considered necessary occasionally.

No attempt has been made in these tables to estimate the amount of various foods taken, or the amount of nitrogen excreted. Such information would have been of considerable value, but the additional labour which it would have entailed could not be efficiently carried out in these cases.

For valuable assistance I have to express my thanks to the house-physicians, clinical assistants, and particularly to the experienced and careful ward sisters. Prolonged clinical observations on the effects of drugs in disease can never be carried out in the exact manner that is possible in laboratories where the lower animals are under observation, but provided this fact is constantly kept before

us, they have a certain value of their own which the artificial circumstances of a laboratory experiment cannot have.

*Explanation of Charts.*

Each chart represents the observations on a separate case of diabetes. It is divided into 'periods' marked alphabetically (A, B, C, D, &c.). Each period, consisting of several days, represents some change in diet or treatment. Alongside each period is placed a number representing its duration in days: these periods will be seen to vary considerably—usually about a week or some multiple of that.

The next three columns give the conditions under which the patient was placed during each period with respect to his three important factors of life, namely (1) Diet, (2) Rest, (3) Drugs.

It will be seen that in most of the cases only one of these factors has been changed at a time, so that there might be no confusion as to which of the two altered factors was associated with any resulting changes.

This statement must be modified as regards factor No. 2, viz. Rest, since it was occasionally found impossible to get patients to submit to complete rest in bed for prolonged periods. As a matter of fact in cases where patients are getting up for a short time daily and are limited in exercise to the precincts of a level hospital ward, the effect is probably small.

In the column marked 'Drug' the dose is always expressed in 'grains per day'; thus '$1\frac{1}{2}$' means $1\frac{1}{2}$ grains given as $\frac{1}{2}$ grain in three doses, unless otherwise stated. 'O.' in that column means that the particular drug given during the preceding period was left off during that period.

'Full' diet means the ordinary hospital diet similar to that given to ordinary patients, consisting of meat, vegetables, bread, butter, milk, sugar, pudding, with no restriction as to any form or quantity of carbohydrate. 'Strict' diet consists of meat, eggs, milk, green vegetables, butter, gluten bread (30 per cent. carbohydrate).

The rest of the chart is divided into two parts. The first part shows three items in each period: (1) the average daily quantity of liquid drunk, in litres; (2) the average daily quantity of urine excreted, in litres; (3) the average daily quantity of sugar excreted, in grammes (100 grammes).

It is important to remember that each of the above numbers is an average for the whole corresponding 'period', and has been obtained by adding together the total daily quantities and dividing by the number of days of that period.

The last column of each chart gives the patient's weight in pounds during each period.

It will be seen that in every case on admission the patient has been placed upon full diet without any restriction as to carbohydrates. This is period A in all cases. This was essential in order to institute comparisons. It is useless to

attempt to gauge the effect of a restricted diet unless one has some idea of the patient's response to a diet with free carbohydrates. The daily results of this full diet were so irregular that it was sometimes found necessary to continue period A for a considerable time, and in one case (Case III), as will be shown later, this continuation of full diet showed a very definite increased tolerance of carbohydrates during the second and third weeks.

During this period (A), in all cases, the patient was kept absolutely in bed, and no special drugs were given. During the next period (B), the diet alone was altered, namely, to a strict diet as defined above (except in Cases II and III, where toasted bread was given). Meanwhile rest in bed was, as a rule, continued and no special drugs were given. In no case was any bad result seen from the sudden alteration of diet. At the end of period B, the diet and rest remaining unchanged (the latter, as a rule, being slightly relaxed in stringency), the particular drug to be tested was begun. Any change in the quantity of this is marked as a fresh period. When the drug was omitted, a period of rest was always given before another drug was tried. In several cases it was impossible to try more than one drug on account of the length of time the patient had already been in hospital.

### *The Effect of Codeia.*

This alkaloid was given in seven of the cases (Cases I, II, III, IV, V, VI, VII, in the last named in small doses only), always in the form of a pill. As a rule the initial dose was one quarter of a grain thrice daily (marked $\frac{3}{4}$ on the charts), which was gradually increased, at varying intervals, by one quarter grain per dose, or by larger amounts, until as much as twelve grains was being taken daily.

*Effect on the Intake of Liquid.* The effect on the intake of liquid varied considerably in different cases. Thus the quantity of liquid drunk was definitely diminished in two cases (Cases IV and V), definitely increased in one case (Case III), indefinite or variable in four cases (Cases I, II, VI, VII). In neither case where it was definitely diminished did the diminution go *pari passu* with the size of the dose. Thus in Case V the most marked diminution was during the first three weeks of taking the drug, when the dose remained small and stationary, viz. $\frac{3}{4}$ grain per day. A further decrease followed the increase of dose to $1\frac{1}{2}$ grains, but a rapid increase up to 9 grains produced no further improvement. In Case IV, on first admission the dose never exceeded $1\frac{1}{2}$ grains daily, and the quantity of liquid remained stationary; on readmission with larger doses the diminution continued up to 6 grains, after which there was no further effect, though the dose was raised to double. In Case I it will be seen that whilst there was a decrease of liquid drunk during the first nineteen days of codeia, yet after the dose reaches $2\frac{1}{4}$ grains daily the quantity of liquid drunk was greater than before its administration at all. In Cases II and III the conditions were not exactly identical with the other cases, in respect to carbohydrates given. Thus in Case II toasted bread

was given up to the end of period D, after which this was omitted and Cheltine bread given in its place. The only diminution in liquid taken began after the omission of toasted bread. In Case III small quantities of toast and potatoes were given during the whole periods B to I, and the quantity of liquid taken was greater with codeia than without.

*Effect on the Quantity of Urine.* The remarks made above as to the effect of codeia on the liquid drunk must apply to a certain extent also to the quantity of urine excreted, since, allowing for a small margin on the one side for liquid taken in every food and more particularly as sauces, gravies, &c., and on the other side for liquid lost by the faeces, sweat, and expired air, we must have a balance between liquid drunk and urine excreted, which is shown in the charts to be fairly constant in each individual. Out of the seven cases under observation the quantity of urine is

diminished in 3 (Cases IV, V (readmission), and VII),
increased in 2 (Cases III and VI),
irregularly affected in 2 (Cases I and II).

As mentioned above, Cases II and III were not on strict diet throughout, Case II not until period E, Case III at no time. They are therefore not strictly comparable, but they emphasize the fact that a very little extra carbohydrate quickly neutralizes any evident effect of codeia on these factors in the disease. In Case I the early, promising effects disappeared completely with increased time and dosage.

*Conclusions.* 1. Codeia in some cases seems to cause a diminished excretion of urine, in others it appears to have no such effect.

2. In some cases a gradually increased dose appears to keep up the effect for many weeks; in others an increase of dose beyond a certain point, varying in different individuals, is either of no further value or even harmful.

*Effect on the Daily Output of Sugar.* Out of the seven cases under observation the daily output of sugar was

diminished in 3 (Cases IV, V, and VII),
increased in 1 (Case VI),
irregularly affected in 3 (Cases I, II, and III).

The same remarks as before apply to Cases II and III with regard to diet. In Case I the increase of output with larger doses is noticeable, and may be compared with the similar rise in Case VI.

*Summary.* 1. In a certain number of cases codeia has a distinct influence in reducing glycosuria, which may be kept up for several weeks or even improved by increasing the dose.

2. In other cases where the effect of small doses ($\frac{3}{4}$ to $2\frac{1}{4}$ grains daily) is ineffectual, larger doses may increase glycosuria.

3. In some cases the effect is apparently quite irregular, if present at all.

*Effect on Body Weight.* Out of seven cases:—

Increase of weight in 5 (Cases I, II, III, IV, and V).

Loss of weight in 2 (Cases VI and VII).

Of the five cases, the maximum increase was in Case V, who put on 10 lb. in ten weeks.

It is evident that the increase in weight during the administration of codeia must not be necessarily attributed to its action alone, if at all. The changed circumstances of the average hospital diabetic on coming into the wards, the regular and suitably nourishing food, and the rest from work and worry may play the most important, or the whole part in this gain of weight.

In support of such a view it will be noticed that in some of the cases a gain in weight began during period B, that is, prior to the administration of codeia. In some of the cases (I, III, VI, and VII) there was an initial loss of weight during full diet, so that the gain of weight under codeia is partly a return to the weight on admission.

On the whole, however, the general effect of codeia seems to be at least not to prevent gain of weight, but in some cases to promote it, as is shown by a decrease in weight following omission of the drug (Case V). It is worth noting that in Cases II, III, and IV some loss of weight was associated with increased doses of codeia, after a previous steady gain for some weeks.

The rapid loss of weight during periods O and P in Case I was associated with the onset of complications (carbuncles, &c.) and preceded the fatal termination.

*General Summary of the Effects of Codeia in Diabetics.* On the whole the definite results obtained in these cases are disappointing. Possibly the doses given were altogether too small. This does not seem an adequate explanation, however, as in more than one case the results have appeared to become less favourable with increased doses. On the other hand, in a certain small number of cases the effects of gradually increased doses have been favourable even over several weeks. It may be said that such a drug as codeia will quickly lose its first sedative effect, hence it can only be of value for a short period. There does not seem any prima facie ground for such a statement. One knows that codeia and other alkaloids of opium may exert their ordinary influences for years provided the quantity is increased, and if that is true of their general effects, it may be equally true of such effects as they have in certain diabetics.

Whether such a perpetual administration of an opium alkaloid is desirable or likely to be beneficial in the long run is beyond the scope of this paper.

I have, however, been struck in these cases by the general absence of craving when the codeia was omitted; in fact, in no case have I had any complaint of such craving.

### *The Effect of Opium.*

Opium, either in the form of Pil. Opii or of Pil. Saponis Co., was given in six cases. In three of these (Cases VII, VIII, and IX) it was tried before any other drug, whilst in three cases (I, II, and VI) it was given to patients who had previously taken codeia, in order that the effects of the two alkaloids might be compared in the same individuals.

The initial dose given varied from $\frac{1}{5}$ grain to 1 grain, thrice daily, and

was usually increased gradually, in one case up to 12 grains daily; in Case VIII the dose was never increased from the initial 3 grains per day.

Case I, whilst apparently making good progress, showed symptoms of commencing acidosis which unfortunately proved fatal; the terminal diminution of urine and sugar shown in the chart marks, therefore, no improvement.

*Effect on the Intake of Liquid.* Out of six cases under observation the quantity of liquid taken in was diminished in three cases (I, VIII, and IX). In three cases (II, VI, and VII) the effect was very slight either way, and, incidentally, in Case VI (period K) the substitution of toast for gluten bread made a distinct increase of liquid drunk. In this case codeia given previously (periods C, D, E, F) had no positive effect on the liquid drunk.

*Effect on the Quantity of Urine.* In two cases (VIII and IX) this was consistently lessened. In Cases II and VII it was distinctly increased. In Case VI it was not markedly affected.

In Case I it remained unaffected until large doses were reached, but as a fatal termination occurred three weeks later this diminution may be looked upon as a terminal one.

*Effect on the Daily Output of Sugar.* In four cases (I, VI, VIII, and IX) this was more or less favourably influenced. In Case VIII, where the dose was constant, the diminution week by week was steadily greater. In Case I the best effect was produced by smaller doses, the quantity increasing with larger ones.

N.B.—The diminution in periods O and P has been referred to already. In Case VI the effect seemed to be progressively good until period K, when it was necessary to alter the carbohydrates.

In two cases (II and VII) the daily output was slightly increased.

*Effect on Body Weight.* In four cases (I, VI, VIII, and IX) there was an increase in body weight. In Cases VIII and IX this was steady and continuous up to the end of the period during which the drug was given, and in each case cessation of the drug was followed by a definite fall in weight.

In Case I the rise was steady and continuous up to period O, that is, two weeks before the man's death. This point will be referred to later.

In Case VI the weight rose steadily until period K (5 days), when the carbohydrate had to be increased; this was followed by a fall of 1·4 kilos, which continued 0·5 kilos lower the next week, then ceased and again a rise of 1·4 kilos took place.

In two cases (II and VII) there was loss of weight. In Case VII the weight, which had been going up slightly for three weeks previously, went steadily down whilst taking opium.

*Summary of the Effects of Opium.* In spite of the fact that one of the patients became worse and died whilst under treatment by opium, the general results obtained with it were on the whole rather more uniformly successful than those obtained with codeia. In three cases (I, II, and VI) codeia had previously been tried, and comparing the results one sees that (in Case I) opium began

to act effectively when codeia in increasing doses had ceased to do so. (Compare the three periods preceding period H in Case I with the three succeeding it.)

It is difficult to say from so few cases whether there is any gain or not by increasing the dose, and if so to what amount. It is certainly not always necessary, at any rate for some time, as is evidenced by the progressive improvement in Case VIII with a stationary dose. Possibly each individual case has its own peculiarity in this respect, and it would at least require a very wide experience before any rules could be laid down.

### *The Effect of Secretin.*

In two cases (VIII and IX) after a period of treatment by opium, the patients were, after about a week's omission of the drug, put upon a preparation of secretin. During the whole time they were taking a 'strict diet' according to the definition previously given. The secretin was prepared according to the following directions given by Moore, Edie, and Abram (*Bio-Chemical Journal*, vol. i, No. 1, p. 32):—

The upper 3 or 4 feet (about 1 metre) of the small intestine of the pig, obtained fresh from the abattoir, is taken and laid open from end to end. The mucous surface is then rapidly and as thoroughly as possible washed free from adherent matter with normal saline or water, but the washing must not be too long continued. As the extract is afterwards sterilized by boiling there is no fear of infection from any slight trace of adherent material. The strip of intestine is then laid with the mucous surface upward upon a plate of clean glass, and the mucous membrane scraped off with a broad blunt knife, the blade being held perpendicularly to the surface, and 5 or 6 inches being cleared at a time.

The scrapings are next passed through a fine sausage machine or disintegrator, from which they come out as a homogeneous, soft, semi-fluid mass. This mass is thoroughly mixed up for about five minutes in a mortar, with an equal volume of a dilute solution of hydrochloric acid, containing about 0·4 per cent. of hydrochloric acid, made by adding 10 c.c. of pure, strong hydrochloric acid to a litre of water. The mixture is then placed in a beaker, and, while being stirred, is raised to the boiling-point.

Finally, sodic hydrate is added until the mixture just remains acid to litmus-paper. The resulting preparation is given by the mouth, either as it is, or after removal of the coarse, precipitated proteid. The solution, if kept in a bottle roughly sterilized by boiling water, will, if left slightly acid, keep well for three or four days. It should not be used later than this because it slowly loses activity, which takes place more rapidly in alkaline solution, for which reason also it is best to keep it in acid solution. The initial dose in each case was 3 drachms daily, and the maximum 9 drachms daily. In one case the treatment extended over thirty-one days, in the other over twenty-six days.

*Effect on the Intake of Liquid.* In both cases there was no diminution: in

Case VIII there was a slight progressive increase, aggravated by a short period during which toasted bread was taken (three days, period M).

*Effect on the Output of Urine.* In Case VIII, after an initial rise, there was a slight diminution followed by a considerable rise during period M, when toasted bread was given.

In Case IX there was progressive diminution, though slight.

*Effect on the Output of Sugar.* In Case VIII there was on the whole an increase of sugar, additionally great during period M. In Case IX the sugar steadily but only slightly diminished.

*Effect on the Body Weight.* In Case VIII this varied irregularly. In Case IX the fall on leaving off opium was not only made up but even went for a time higher.

*General Remarks on Secretin.* Given in the above-mentioned doses there was no very marked effect. In Case IX there was slight improvement in every respect, whilst in Case VIII there was none. The patients complained of its unpleasantness.

### *The Effect of Aspirin.*

In Case VIII this was given for twenty-seven days (1 drachm daily). No definite effect was produced on the intake of liquid, quantity of urine, sugar output, or body weight.

### *Effect of Full Diet on the Body Weight.*

In every case the patient on admission was put on to unrestricted ordinary full diet, consisting of meat, bread, potatoes, puddings, sugar, milk, tea, and butter. He was kept absolutely in bed and no special drugs were given.

One might expect that under such conditions some fairly constant effect would be produced upon the body weight, or at least that the effect would be fairly definitely associated with the severity of the case, or perhaps bear some relation to the total daily output of sugar or the percentage of the same. In six out of the nine cases, however, in which the patient was weighed on admission and again at intervals during the period A when under the conditions described above, quite irregular results occurred, as is shown in the following table (Chart 10). In all these cases the patient was weighed on admission, and again under exactly similar conditions as to clothing, scales, &c., either at the end of period A, or at varying intervals during that time, as in Case III.

How variable were the results is shown by the two extreme cases, viz. Case VIII, who put on weight at the rate of 290 grammes per day whilst excreting 640 grammes of sugar per day, whilst Case VI lost weight at the rate of nearly 500 grammes per day whilst only excreting 150 grammes of sugar during the same time; whilst as a medium point Case II showed no loss or gain in weight. Of particular interest is Case III in this connexion. His

period A was prolonged to three weeks on account of the alteration in his behaviour to full diet. Whilst during the first week loss of flesh was marked, yet during the second and third weeks of full diet the sugar excretion diminished and he began gradually to put on flesh again. In fact, this patient during the third week of full unrestricted diet passed almost as small a daily average quantity of sugar as during the next period (B), when carbohydrates were cut off (viz. 250 grammes).

*Short Notes of Cases.*

*Case I.* W. G. Male, aged 42, tool hardener. Had suffered from influenza. Admitted to Sheffield Royal Hospital, January 12, 1907. Three years ago he began to suffer from thirst and polyuria, which had continued ever since. Two years ago his sight began to fail and he had to wear glasses. Eighteen months ago his teeth began to come out. He complained of pain in the left iliac region. The skin was very dry. Tongue tremulous and coated. Pupils reacted sluggishly. Left disk small and white. He seemed to progress favourably until March 14, when a carbuncle formed on the neck. Another began on April 1, and a third on the 24th. On April 1 he became somewhat drowsy and diacetic acid was present in the urine. On April 30 the knee-jerks were absent. He died on May 1, 1907.

*Case II.* A. W. Female, aged 52, married. She was admitted to the Sheffield Royal Hospital on May 15, 1906. She had typhoid fever in November, 1905. One brother died of consumption. Six months ago, that is December, 1905, she had pain in the left side, a rash on the body, joint pains, thirst, and polyuria. She also had pain in the eyes and amenorrhoea. The skin was irritable, but moist. Tongue tremulous, glazed. Disks pale, retinal haemorrhages. Knee-jerks absent. Discharged October 5, 1906.

*Case III.* H. W., aged 51, miner, was admitted to Sheffield Royal Hospital on July 5, 1906. No history of previous illnesses. Mother died of dropsy. He had taken whisky freely. Six months ago, cramp in the legs, which swelled; thirst, increased appetite, polyuria. Eyes painful when reading. Tongue furred, no retinal changes. Knee-jerks absent; plantar reflexes present; diminished faradic irritability of leg muscles; slight peripheral neuritis. Discharged September 29, 1906.

*Case IV.* H. A., aged 41, traveller, was admitted to Sheffield Royal Hospital on May 19, 1908. Had smallpox in 1904, also pleuro-pneumonia five times. Alcoholic history. Father died of 'brain fever'. Six months ago, sweet taste in mouth, great thirst, itching of skin, polyuria (13 pints a day), increased appetite. He had lost two stone in weight. The skin had been dry since illness, but was now moist. Eyes normal. Knee-jerks present. He was discharged on June 25, 1908. Readmitted July 26, and again discharged October 16, 1908. Since being discharged he has attended as an out-patient and continues in the same condition.

*Case V.* P., male, admitted to Sheffield Union Hospital, January 30, 1907. No previous illnesses, fairly heavy drinker. No family history of diabetes or other definite condition. Four months ago, intense thirst, polyuria, rapid loss of weight—from 13 stone to 10 stone 10 lb. Had been weak for a year. Eyesight failing for some time. Skin very dry. Mental condition very irritable. Knee-jerks not obtained.

*Case VI.* L. G., aged 26, married, was admitted to the Sheffield Royal Hospital on January 12, 1907. She had suffered from anaemia. Father was

consumptive. One year ago, great thirst, polyuria, pain in the calves, rapid loss of weight. The skin was dry. Tongue dry, white fur. Discharged May 15, 1907.

*Case VII.* A. B., aged 46, married, was admitted to the Sheffield Royal Hospital on August 10, 1906. She had typhoid fever in 1901. A moderate alcohol drinker. One brother died of tubercular hip-disease. For four months she had had polyuria, great thirst, and sweating. The eyes had been going dim. Skin dry. Tongue dry. Knee-jerks not obtained. Fundi oculorum normal. Discharged October 27, 1906, in practically same condition.

*Case VIII.* W. S., aged 34, labourer, was admitted to the Sheffield Royal Hospital on April 16, 1907. No history of previous illnesses. Family history, nothing definite. Two weeks ago, great thirst, polyuria, pain in left side of chest. Skin dry. Tongue moist. Eyes normal. Knee-jerks absent. No other abnormal physical signs. Discharged August 27, 1907.

*Case IX.* K. T., aged 28, single, was admitted to Sheffield Royal Hospital on March 13, 1907. Previous illnesses: influenza; dropsy in 1903 and again in 1906. Father and mother died of 'heart failure'. One sister had rheumatism. Three months ago, great thirst, polyuria, and increased appetite. One month ago, pain in the right lumbar region. Skin very dry. Tongue clean and moist. Boils on hand and face. No other abnormal physical signs. Discharged July 19, 1907. Diacetic acid in urine from May 22 to July 19.

*Case I.* CHART No. 1.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Quantity. | Daily Average: Intake of Water. | Daily Average: Output of Urine. | Daily Average: Output of Sugar. | Body Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 9 | Full | Bed | O. | | 6750 | 6500 | 435 | 46·8–44·9 |
| B | 15 | Strict | „ | O. | | 4250 | 4200 | 230 | 46·3 |
| C | 8 | „ | Up | Codeia | ¾ grains | 3800 | 3400 | 200 | 47·2 |
| D | 11 | „ | „ | „ | 1½ „ | 3600 | 3400 | 220 | 47·7 |
| E | 7 | „ | „ | „ | 2¼ „ | 4450 | 4100 | 205 | 49 |
| F | 14 | „ | „ | „ | 3 „ | 4500 | 4500 | 225 | 49·5 |
| G | 7 | „ | „ | „ | 4 „ | 4350 | 4750 | 260 | 49·7 |
| H | 7 | „ | „ | O. | | 4825 | 4800 | 275 | 49·5 |
| I | 7 | „ | „ | Opium | ¾ grains | 4200 | 4600 | 285 | 49 |
| J | 7 | „ | „ | „ | 1½ „ | 4400 | 5000 | 185 | 49·9 |
| K | 7 | „ | „ | „ | 2¼ „ | 4500 | 4950 | 150 | |
| L | 7 | „ | „ | „ | 3 „ | 4500 | 5000 | 175 | 50·1 |
| M | 14 | „ | „ | „ | 6 „ | 4300 | 5050 | 255 | 50·8 |
| N | 8 | „ | „ | „ | 9 „ | 4300 | 5150 | 260 | 51·3 |
| O | 7 | „ | „ | „ | 12 „ | 3825 | 4450 | 165 | 49 |
| P | 7 | „ | „ | „ | 9 „ | 2550 | 3650 | 145 | 45·9 |

Died.

*Case II.* CHART No. 2.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Quantity. | Daily Average: Intake of Water. | Daily Average: Output of Urine. | Daily Average: Output of Sugar. | Body Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 13 | Full | Bed | O. | | 3000 | 1900 | 70 | 53·6–53·8 |
| B | 21 | Strict with Toast | „ | O. | | 3150 | 2500 | 108 | 54·5 |
| C | 18 | „ | Up | Codeia | ¾ grains | 3750 | 2575 | 115 | 54·7 |
| D | 10 | „ | „ | „ | 1½ „ | 3225 | 3000 | 135 | 55·4 |
| E | 9 | Omit Toast | „ | „ | 2¼ „ | 3275 | 2775 | 105 | 55·9 |
| F | 7 | „ | „ | „ | 3 „ | 3400 | 2675 | 118 | 56·3 |
| G | 21 | „ | „ | „ | 4½ „ | 2525 | 1850 | 65 | 55·9 |
| H | 4 | „ | „ | O. | | 1800 | 1275 | 30 | 53·1 |
| I | 9 | „ | „ | Opium | 1½ grains | 1900 | 1375 | 38 | 52 |

*Case III.* CHART No. 3.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 20 | Full | Bed | O. | | 4375 | 4700 | 430 | 53·6-49 |
| B | 8 | Restricted Toast, Potato | ,, | O. | | 3300 | 3750 | 250 | 50·8 |
| C | 14 | ,, | Up | Codeia | $\frac{3}{4}$ grains | 3500 | 3500 | 230 | 52·2 |
| D | 8 | ,, | ,, | ,, | $2\frac{1}{2}$ ,, | 4075 | 4400 | 330 | 52·7 |
| E | 6 | ,, | ,, | ,, | 3 ,, | 4150 | 4050 | 240 | 52·9 |
| F | 8 | ,, | ,, | ,, | $4\frac{1}{2}$ ,, | 4400 | 4200 | 212 | 53·1 |
| G | 9 | ,, | ,, | ,, | 6 ,, | 4300 | 4400 | 280 | 53·6 |
| H | 8 | ,, | ,, | ,, | $7\frac{1}{2}$ ,, | 3800 | 3400 | 180 | — |
| I | 4 | ,, | ,, | ,, | 9 ,, | 3775 | 4100 | 275 | 51·3 |

*Case IV.* CHART No. 4.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 7 | Full | Bed | O. | | 3550 | 2650 | 210 | 47·5 |
| B | 8 | Strict | ,, | O. | | 3300 | 2175 | 75 | 48·3 |
| C | 8 | ,, | Up | Codeia | $\frac{3}{4}$ grains | 3025 | 1925 | 45 | 47·7 |
| D | 5 | ,, | ,, | ,, | $1\frac{1}{2}$ ,, | 3225 | Record | unreliable | 48·8 |
| E | 9 | ,, | ,, | ,, | $1\frac{1}{2}$ ,, | 3225 | 2450 | 40 | 49 |
| | | | | Left hospital for a time | | | | | |
| B | 23 | Strict | Bed | O. | | 3400 | 2450 | 110 | 49·5 |
| C | 8 | ,, | Up | Codeia | $2\frac{1}{4}$ grains | 3150 | 2550 | 100 | 50·1 |
| D | 7 | ,, | ,, | ,, | 3 ,, | 3125 | 2350 | 125 | 50·6 |
| E | 17 | ,, | ,, | ,, | 6 ,, | 2475 | 2050 | 50 | 50·8 |
| F | 11 | ,, | ,, | ,, | 9 ,, | 2525 | 1650 | 30 | 50·8 |
| G | 17 | ,, | ,, | ,, | 12 ,, | 2500 | 1800 | 70 | 49·9 |

*Case V.* CHART No. 5.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 7 | Full | Bed | O. | | 4250 | 4975 | 325 | ? |
| B | 7 | Strict | ,, | O. | | 5650 | 5275 | 250 | ? |
| C | 7 | ,, | ,, | Codeia | ¾ grains | 5100 | 4250 | 205 | 59·5 |
| D | 14 | ,, | Up | ,, | ¾ ,, | 4700 | 4525 | 240 | 60·9 |
| E | 7 | ,, | ,, | ,, | 1¼ ,, | 3775 | 3850 | 190 | 62·7 |
| F | 14 | ,, | ,, | ,, | 2¼ ,, | 3775 | 3950 | 180 | 62·7 |
| G | 21 | ,, | ,, | ,, | 6 ,, | 3800 | 3200 | 150 | 64 |
| H | 7 | ,, | ,, | ,, | 9 ,, | 3750 | 3625 | 112 | 64 |
| I | 6 | ,, | ,, | O. | | 3550 | 3725 | unreliable | 63·6 |
| J | 12 | Bread | ,, | ,, | | 3800 | 3200 | 112 | 61·8 |
| K | 12 | Strict | ,, | ,, | | 3550 | 3450 | 90 | 59·5 |

*Case VI.* CHART No. 6.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 8 | Full | Bed | O. | | 2400 | 2375 | 150 | 45·9–43·6 |
| B | 8 | Strict | ,, | O. | | 2090 | 1875 | 125 | 44 |
| C | 7 | ,, | ,, | Codeia | ¾ grains | 2100 | 2050 | 123 | 43·3 |
| D | 11 | ,, | Up | ,, | 1½ ,, | 2245 | 2000 | 120 | 43·3 |
| E | 10 | ,, | ,, | ,, | 2¼ ,, | 2200 | 2350 | 135 | 43·6 |
| F | 8 | ,, | ,, | ,, | 3 ,, | 2400 | 2475 | 170 | 43·6 |
| G | 8 | ,, | ,, | O. | | 2350 | 2500 | 200 | 43·8 |
| H | 6 | ,, | ,, | Opium | 1½ grains | 2350 | 2650 | 170 | 44·2 |
| I | 7 | ,, | ,, | ,, | 3 ,, | 2300 | 2300 | 123 | 44·2 |
| J | 9 | ,, | ,, | ,, | 4½ ,, | 2750 | 2325 | 170 | 45 |
| K | 5 | Bread | ,, | ,, | 6 ,, | 3200 | 3400 | 206 | 43·6 |
| L | 9 | Strict | ,, | ,, | 6 ,, | 2000 | 1950 | 90 | 43·1 |
| M | 9 | ,, | ,, | ,, | 3 in 3 doses | 2650 | 2300 | 160 | 43·1 |
| N | 3 | ,, | ,, | ,, | 3 in 6 doses | 2600 | 2700 | 196 | 44·5 |
| O | 5 | ,, | ,, | ,, | 3 in 3 doses | 2450 | 2600 | 180 | ? |

*Case VII.* CHART No. 7.

| Period | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 6 | Full | Bed | O. | | 2525 | 2875 | 210 | 38·1 |
| B | 14 | Strict | „ | O. | | 1900 | 1950 | 85 | 37 |
| C | 8 | „ | Up | O. | | 2200 | 1800 | 90 | 37·4 |
| D | 8 | „ | „ | Opium | $\frac{3}{5}$ grains | 2300 | 2475 | 100 | 38·1 |
| E | 8 | Omit Milk | „ | „ | $\frac{9}{10}$ „ | 2350 | 2250 | 80 | 37·9 |
| F | 6 | „ | „ | „ | $1\frac{1}{5}$ „ | 2450 | 2475 | 110 | 37·4 |
| G | 14 | „ | „ | O. | | 2200 | 2350 | 112 | 37·2 |
| H | 11 | „ | „ | Codeia | $\frac{3}{4}$ grains | 2375 | 2175 | 104 | 36·5 |

*Case VIII.* CHART No. 8.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 6 | Full | Bed | O. | | 7900 | 8500 | 640 | 53·1 |
| B | 13 | Strict | „ | O. | | 6000 | 6700 | 365 | 54·5 |
| C | 7 | „ | Up | Opium | 3 grains | 4400 | 5600 | 358 | 55·1 |
| D | 7 | „ | „ | „ | „ | 4100 | 5200 | 338 | 55·6 |
| E | 7 | „ | „ | „ | „ | 4050 | 4700 | 315 | 55·4 |
| F | 7 | „ | „ | „ | „ | 4000 | 4500 | 318 | 56·7 |
| G | 7 | „ | „ | „ | „ | 3750 | 4500 | 300 | 56·9 |
| H | 5 | „ | „ | „ | „ | 3600 | 4000 | 260 | 58·1 |
| I | 7 | „ | „ | O. | | 4600 | 5100 | 325 | 57·2 |
| J | 5 | „ | „ | Secretin | ʒiij | 4600 | 5500 | 360 | 56·9 |
| K | 5 | „ | „ | „ | ʒvj | 4750 | 4900 | 320 | 57·9 |
| L | 5 | „ | „ | „ | ʒijss. | 4900 | 4800 | 320 | |
| M | 3 | Toast | „ | „ | „ | 5450 | 6100 | 420 | 57·2 |
| N | 13 | Strict | Bed | „ | „ | 5400 | 5600 | 365 | 56·7–57·9 |
| O | 27 | „ | „ | Aspirin | ʒj | 5600 | 5700 | 375 | 58·8–57·9 |

*Case IX.* CHART No. 9.

| Period. | Days. | Diet. | Rest. | Drug. | Daily Amount. | Daily Average Quantity of Water. | Urine. | Sugar. | Weight. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | c.c. | c.c. | grammes. | kilos. |
| A | 7 | Full | Bed | O. | | 3325 | 3300 | 275 | 45·3 |
| B | 8 | Strict | „ | O. | | 4100 | 3200 | 180 | 47·2 |
| C | 8 | „ | „ | Opium | 3 grains | 3350 | 2750 | 158 | 48·1 |
| D | 18 | On 2 days Toast | „ | „ | 4½ in 3 doses | 2850 | 2800 | 172 | 48·1 |
| E | 12 | Strict | Up | „ | 4½ in 6 doses | 2700 | 2450 | 140 | 48·6 |
| F | 40 | On 2 days Toast | „ | „ | 4½ in 3 doses | 2900 | 2550 | 175 | 50·4 |
| G | 9 | Strict | „ | O. | | 3000 | 3100 | 212 | 49·9 |
| H | 9 | „ | „ | Secretin | ℥iij | 3200 | 2850 | 205 | 49·7 |
| I | 17 | „ | „ | „ | ℥ijss. | 3000 | 2500 | 165 | 51–50·4 |

CHART No. 10.

*Effect of Full Diet on Body Weight. Total Sugar Excretion and Percentage in Urine.*

| Case No. | | Table showing Daily Average Percentage of Sugar. | Output of Sugar. | Variation in Weight. Gain. | Loss. |
|---|---|---|---|---|---|
| 1 | | 6·6 | 430 grammes | 0 | −201 grammes |
| 2 | | 3·5 | 70 „ | 0 | 0 |
| 3. | First Week | 6·7 | 366 „ | 0 | −643 grammes |
| | Second Week | 7·2 | 306 „ | +130 grammes | 0 |
| | Third Week | 6·3 | 250 „ | +151 „ | 0 |
| 6 | | 6·4 | 150 „ | 0 | −498 grammes |
| 8 | | 7·5 | 640 „ | +290 „ | 0 |
| 9 | | 7·3 | 275 „ | +130 „ | 0 |

# A CONTRIBUTION TO THE STUDY OF CONGENITAL FAMILY CHOLAEMIA

By ROBERT HUTCHISON and P. N. PANTON

In his textbook of *Diseases of the Liver* (3rd ed. 1885, p. 481), Murchison records, under the heading 'Hereditary Jaundice and Gout', the following case which he says he had the opportunity of seeing, through the kindness of Dr. Moxon, in February, 1875 :—

Robert J., aged 30, says he was born yellow and that he has been jaundiced as long as he can remember. He had never been robust, but from age of 17 to 27 he had been in habit of walking twenty miles a day, exposed to all kinds of weather and eating all sorts of food. At 21 he had been laid up for six weeks with a febrile attack ; and at 27 he had another illness, after which he had led a more sedentary life, but had continued to drink about three pints of beer daily. From 27 up to the date of his visit to me he had suffered much from gout in fingers and toes, which had always been relieved by iodide of potassium. Urine had deposited a copious sediment as long as he could remember. Four months before seeing me he had left off beer and all stimulants, and during that time he had become much fairer than ever before.

I made following notes: Body fairly nourished, and is leading an active life. Has decided yellowness of skin and conjunctivae. Urine contains abundance of lithates, and presents distinct reaction of bile-pigment. Liver slightly enlarged, measuring $4\frac{3}{4}$ inches in right mamillary line, not tender. Appetite good ; occasional flatulence ; bowels sluggish ; motions fairly coloured with bile. Always has giddiness on looking up, and formerly had it whenever he got up or lay down.

On Oct. 9, 1876, Dr. Moxon wrote to me as follows: R. J. is still a teetotaller ; but urine contains bile-pigment as before and jaundice persists.

R. J. has a brother, two years and eight months older than himself, who has also been deeply jaundiced all his life, and in Feb. 1875 was laid up with gout. In October, 1876, I heard from Dr. Moxon that this brother continued to drink beer and was still very much jaundiced.

The mother of these two brothers died at the age of 54. She had been in the habit of drinking malt liquor freely, and for fourteen years before death she had been a great sufferer from gout, her feet and every one of her finger-joints being greatly deformed with it. During same period she had been continuously jaundiced, the 'whites' of her eyes being deep yellow, and she had had frequent bilious attacks. She had borne seven children, but five had died soon after birth or in early infancy. An only brother had died of consumption ; but her father had suffered greatly from gout and liver-complaints.

Father of R. J. is still (Oct. 1876) alive and healthy ; never had gout nor jaundice.

I learn from Dr. Moxon also that both R. J. and his brother have had several children, all of whom 'became deeply jaundiced two days after birth, the colour being—eyes, body, and whole frame—as deep as possible, but disappearing after about a month'.

[Q. J. M., July, 1909.]

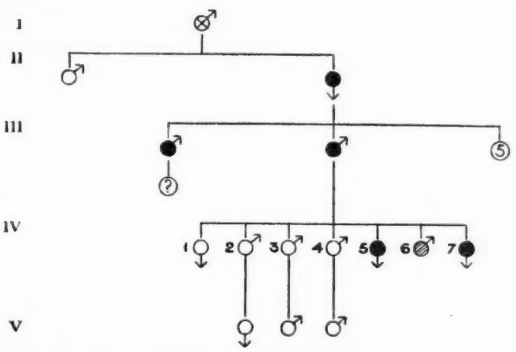
Murchison comments upon this case as follows:—

'Although there may be doubts as to whether the yellowness of the children of the third generation was true jaundice, there can be no question as to its reality in the case of the mother and her two sons. It must be admitted that the pathology of the jaundice in these cases is obscure. It is clear that there is little or no obstruction of the bile-duct; and the most probable view is that the liver either secretes an excess of bile, or is in a permanent state of congestion. But whatever be its pathology, its intimate relation to gout is interesting in relation to the view which I shall hereafter submit to your notice, that gout has its origin in functional derangement of the liver.'

Murchison's patient (R. J.) died at the age of 59 (cause unknown). His widow, who is still alive and healthy and has not married again, states that she has had altogether seven children, all of whom 'were born yellow'. One of these (a boy) died when ten months old; he was always delicate and 'anaemic'. The others are all living. Of these the eldest (a daughter) and three sons who followed her in order are not jaundiced. Two of the daughters (the fifth and seventh children) are both jaundiced and form the subject of this communication; the boy who died in infancy came between them.

Her three sons are all married, and each has one child (a daughter in the case of one; sons in that of the others, and none of these is yellow), and she states, also, that the children of her husband's brother are not jaundiced.

The family tree, so far as it can be traced, may therefore be represented thus:—




The symbols are those recommended for use in the 'Treasury of Human Inheritance'.

Thus ♂♀ Male and female unaffected by the characteristic.

●♂●♀ Male and female affected by the characteristic.

⊘♂ An individual for whom presence or absence of the characteristic cannot be asserted.

⊗♂ An individual with a disease which may possibly be associated with the characteristic.

○ An individual of unknown sex.

(?) Children of unknown number.

(5) Five children of unknown sex.

The present condition of the two daughters referred to above, neither of whom is married, is as follows:—

*Case I.* Louise J., aged 27, had been yellow from birth. Since her eleventh year had been subject at intervals to attacks of severe abdominal pain resembling biliary colic, after which she was always more deeply yellow. No other illness of importance.

The patient was well developed and fairly nourished. She was very distinctly jaundiced but not appreciably anaemic. The spleen was enlarged, reaching halfway to the umbilicus. The liver was distinctly palpable, firm and slightly irregular. The other organs were normal. The faeces were normal in colour. The urine was heavily loaded with lithates (she says it was always so), and contained no albumin. A specimen was examined as regards pigments by Dr. A. E. Garrod, who kindly reported as follows:—

'The specimen of urine examined had a deep orange colour, chiefly due to uroerythrin in solution. It deposited a copious sediment of urates, deeply stained with *uroerythrin*, which gave to the sediment a deep pink colour.

'The presence of bile pigment was excluded by the negative result of Huppert's test. 800 c.c. of urine were precipitated with barium chloride and hydrate. The precipitate was filtered off and was suspended in alcohol acidified with hydrochloric acid. The acidified alcohol with the precipitate in suspension was heated on a water bath, but no trace of green colour developed.

'Urobilin was present in abundance in the urine, and was extracted by the ether-chloroform method. When some 100 c.c. of urine, acidified with acetic acid, were shaken with amylic alcohol, the amylic extract did not show the absorption bands of haematoporphyrin, and that pigment was presumably not present in more than the normal traces.

'Indoxyl sulphate was present in moderate amount.

'The pigmentation of this urine is such as is seen in cases of chronic hepatic disease, such as cirrhosis hepatis, save that in such diseases there is usually a conspicuous increase of haematoporphyrin beyond the normal trace.'

An examination of the blood gave the following results:—

| | |
|---|---|
| Red cells | 3,937,500 per c.mm. |
| Haemoglobin | 80 per cent. |
| Colour index | 1·0 |
| White cells | 5,420 |

*Differential Count*:—

| | |
|---|---|
| Polynuclear neutrophils | 63·1 per cent. |
| Neutrophilic myelocytes (Ehrlich type) | 0·3 " " |
| Eosinophils | 0·9 " " |
| Mast cells | 1·0 " " |
| Finely basophilic cells | 0·2 " " |
| Small lymphocytes | 24·9 " " |
| Large lymphocytes | 4·5 " " |
| Large hyalines | 5·1 " " |
| | 100 |

7 normoblasts and 3 megaloblasts seen while counting 1000 leucocytes. Macrocytes fairly numerous. Some polychromatophilic degeneration present. Fresh blood shows normal rouleaux formation and practically no poikilocytosis. Bile present in the serum.

*Case II.* Florence J., aged 22, was born 'yellow' and had been 'anaemic' all her life. When she was twelve years old a doctor said that 'the spleen was

affected'. No other illness of importance. No attacks of abdominal pain. Had frequently had epistaxis.

She was a well-developed girl, extremely pale, the skin being of a somewhat chlorotic tint, the conjunctivae very faintly lemon-coloured. No signs of congenital lues. Slight oedema of the ankles at times. The spleen was greatly enlarged, reaching down to the umbilicus, firm and very slightly irregular on the surface. The liver was just palpable and appeared firm and slightly rough. No ascites. Faeces of normal colour. Urine clear, contained no albumin and no bile pigment or bile salts. No urobilin reaction obtainable directly with the urine, but a faint, though quite definite, absorption band appeared after standing for twenty-four hours. The heart showed haemic murmurs.

*Blood examination*:—

| | |
|---|---|
| Red cells | 2,600,000 per c. mm. |
| Haemoglobin | 45 per cent. |
| Colour index | 0·8 |
| White cells | 4,880 |

*Fresh Blood.* Rouleaux formation poor. Poikilocytosis present, also macrocytes and microcytes. Blood platelets scanty.

*Serum.* Strongly bile-tinged and gave reaction for bile-pigments.

*Differential count*:—

| | | |
|---|---|---|
| Polynuclear neutrophils | 59·8 | per cent. |
| Small lymphocytes | 25·0 | ,, ,, |
| Large lymphocytes | 3·4 | ,, ,, |
| Large hyalines | 5·2 | ,, ,, |
| Eosinophils | 5·2 | ,, ,, |
| Mast cells | 0·6 | ,, ,, |
| Finely basophilic cells | 0·4 | ,, ,, |
| Neutrophilic myelocytes | 0·4 | ,, ,, |
| | 100 | |

Six normoblasts and four megaloblasts seen while counting 500 leucocytes. Polychromatophilic degeneration present, and well marked in a few red cells.

*Commentary.*

It is evident that we have here to do with two cases of congenital family cholaemia, and that the case described by Murchison was an example of the same condition occurring in the preceding generation. It is noteworthy, however, that in Murchison's case no mention is made of any enlargement of the spleen, and bile-pigment is said to have been present in the urine, whereas in the two later cases the jaundice is of the acholuric variety. A case of family jaundice with bile-pigment in the urine has, however, been described by Gilbert, Castaigne, and Lereboullet, so that acholuria does not appear to be a constant feature of the disease. We do not propose to discuss fully the pathology of this condition, as it has been dealt with in a recent paper by Hawkins and Dudgeon, but the following investigations on the blood of our patients, which were made by one of us on the same lines as those adopted by these authors, are of interest as confirming the views of those who believe that the jaundice in these cases is of haemolytic origin.

*Experiments.*

In the first place the sera were tested for the presence of haemagglutinins and of haemolysins. The technique employed was the same as that described in the paper of Hawkins and Dudgeon, and in neither case was any haemolytic or agglutinating effect produced by the admixture of the patient's serum with normal washed red corpuscles.

The absence of any haemolytic property in the sera agrees with the observations of Hawkins and Dudgeon. These authors, however, found haemagglutinins to be present in their cases, and, further, these agglutinins appeared to be specific in so far as they were removed by saturating the patients' sera with normal red cells, but not with the red cells of a similar case. In both the cases described here, the serum was tested on more than one occasion at intervals of several months upon different varieties of normal red cells, in each instance with negative results, so that there can be no doubt that the presence of haemagglutinin in the serum is not a constant feature of this condition.

Tests were also made upon the resistance of the blood to graduated strengths of saline solution, and the results agreed with those of previous observers in that the red cells of these cases were more readily haemolysed than those of normal blood. The tests were made by adding blood to saline solutions of varying strength, and comparing the percentages of sodium chloride in which haemolysis ceased in the case of the patient and of a normal individual, the observations upon the normal and the abnormal blood being carried out simultaneously. In Case I, the blood of the patient was compared with normal blood, with the blood of a case of splenomegaly, and with the blood of a deeply jaundiced woman of 53 years, who had been in that condition for four years. The splenomegaly case was a woman with an extremely large spleen, and the blood changes of an ordinary secondary anaemia with leucopenia; the last case had jaundice of uncertain origin, and was chosen in order to eliminate the possibility that the presence of bile in the serum might influence the fragility of the red cells. As may be seen from Table I, the blood of the jaundiced woman and of the woman with splenomegaly did not deviate from the normal, while the blood of Case I showed evidence of haemolysis in dilutions up to 0·6 per cent. of sodium chloride.

TABLE I.

| NaCl % | NORMAL. | CHRONIC JAUNDICE. | SPLENOMEGALY. | CASE I. |
|---|---|---|---|---|
| 0·1 | Complete Haemolysis | Complete Haemolysis | Complete Haemolysis | Complete Haemolysis |
| 0·2 | " " | " " | " " | " " |
| 0·3 | " " | Partial Haemolysis | Partial Haemolysis | " " |
| 0·4 | Tinge | Tinge | Tinge | " " |
| 0·5 | Nil | Nil | Nil | Partial Haemolysis |
| 0·6 | " | " | " | Tinge |
| 0·7 | " | " | " | Nil |
| 0·8 | " | " | " | " |
| 0·9 | " | " | " | " |
| 1·0 | " | " | " | " |

In Case II the blood of the patient was compared with normal blood only, and similar evidence of the fragility of the red cells was obtained.

TABLE II.

| NaCl % | NORMAL. | CASE II. |
|---|---|---|
| 0·1 | Complete Haemolysis | Complete Haemolysis |
| 0·2 | ,, ,, | ,, ,, |
| 0·3 | Partial Haemolysis | ,, ,, |
| 0·4 | Faint tinge | ,, ,, |
| 0·5 | Nil | Partial Haemolysis |
| 0·6 to 2·0 | ,, | Nil |

The examination of the blood in these cases would seem to show that whatever may be the ultimate cause of the condition, one factor of considerable importance is the production of defective red cells. This defective nature of the cells is shown not only by the presence of red cells of abnormal shape, size, and staining reactions, and of nucleated red cells, but also by the increased fragility of the cells when exposed to a medium, the salt content of which differs but little from the normal. Whatever relation this hereditary transmission of defective red cells bears to the jaundice which accompanies the condition, it is apparent that the fragility of the cells is not the effect of the bile in the serum.

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## CRITICAL REVIEW

# THE EXCRETION IN THE URINE OF SUGARS OTHER THAN GLUCOSE

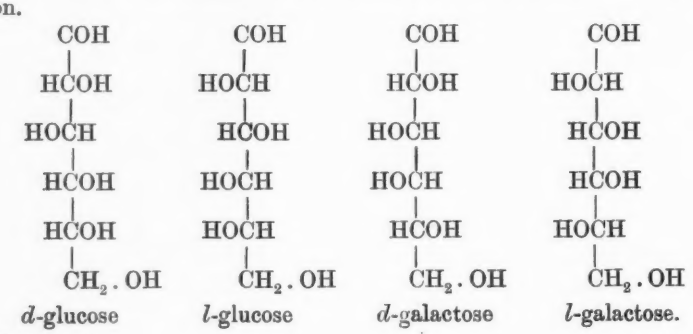
By ARCHIBALD E. GARROD

Glycosuria is so common a symptom, and one possessing so much importance as the most obvious sign of the morbid states which are grouped under the name of diabetes mellitus, that it is in no way surprising that the excretion in urine of sugars other than glucose, which can lay no claim to a like clinical importance, has attracted comparatively little attention from medical men. Nevertheless such forms of mellituria, to employ a name applicable to the excretion of sugars of all kinds, are by no means devoid of interest from the clinical as well as from the pathological standpoint, and it is the aim of this review to summarize the knowledge which has been gained, chiefly in recent years, of the methods by which the several kinds of sugars may be recognized and distinguished from each other, and of the significance which attaches to each.

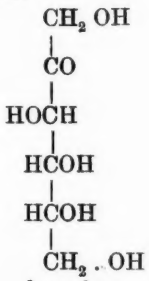
The sugars which call for our consideration differ from each other in various ways. Most of them belong to the hexose group, being built up upon a chain of six carbon atoms, as is glucose itself, and are either monosaccharid members of this group, having the common formula $C_6H_{12}O_6$, or disaccharids, i.e. anhydrides formed by the combination of two monosaccharid molecules either of the same or different kinds, and having the formula $C_{12}H_{22}O_{11}$.

Thus maltose is a disaccharid formed from two molecules of glucose with the loss of a molecule of water, and lactose is also a disaccharid formed from glucose and galactose.

The difference between glucose and galactose, which is merely a matter of the arrangement of the hydroxyl groups upon the carbon chain, is shown in the following formulae, which also indicate the still more subtle differences which separate the dextro- and laevo-rotatory forms of each of the sugars in question.



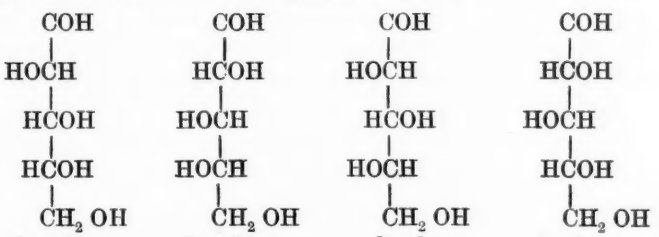
Laevulose, on the other hand, although also a hexose and a monosaccharid, differs from glucose in a far more conspicuous manner; for whereas glucose belongs to the aldose class, and has an aldehyde grouping upon one of its terminal carbon atoms, laevulose is a ketose, and carries a ketone grouping upon its penultimate carbon atom.



laevulose.

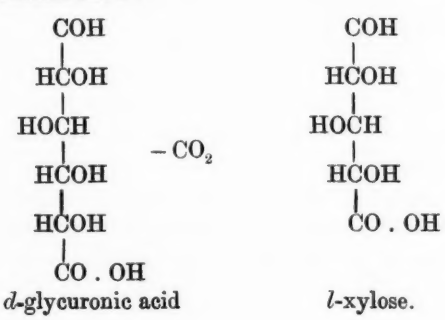
The disaccharid composed of glucose and laevulose, the familiar saccharose or cane sugar, differs from the disaccharids previously mentioned in that the aldehyde and ketone groupings of the constituent sugars are somehow sheltered in combination, so that it lacks the reducing property which is so prominent a quality of most members of the group of sugars.

The pentoses, or sugars built upon a chain of five carbon atoms, will also call for consideration, for two members of this family, arabinose and xylose, play parts in animal as well as in vegetable metabolism.



*d*-arabinose *l*-arabinose *d*-xylose *l*-xylose.

Glycuronic acid, which appears in urine in combination with certain drugs and products derived from the alimentary canal, is closely related to xylose, as the following formulae show:—



*d*-glycuronic acid *l*-xylose.

and such compound glycuronates have to be taken into account as reducing constituents liable to be mistaken for sugars.

The nomenclature of the pentoses is apt to be confusing unless the principle upon which it is based be understood. The letters *d*- and *l*- indicate in their case their relationship to sugars of the hexose class, and not their own optical properties: and as a matter of fact *l*-arabinose and *l*-xylose are dextro-rotatory, whereas *d*-arabinose and *d*-xylose rotate the polarized ray to the left.

In a single case Rosenberger found in the urine a sugar which he believes to have been a member of the heptose, or seven-carbon series. Previously such sugars had not been recognized as constituents of the tissues of animals.

In some instances the sugars mentioned in the above summary have been met with in association with glucose, usually in relatively small amounts. Sometimes one or other of them occurs alone in the urine and bears witness to an error of carbohydrate metabolism wholly distinct from that which gives rise to glycosuria. Moreover, it sometimes happens that the excretion of a particular sugar, such as laevulose, appears to have a wholly different significance in different cases, its presence in the urine being due to quite distinct metabolic derangements.

### *Lactosuria.*

That women often excrete a sugar in their urine during the period of lactation has long been known, and the fact was recorded by Blot (1) as long ago as the year 1856. The actual nature of the sugar so excreted was first definitely determined by Hofmeister (2) in 1877, who showed that it was lactose. Urine which contains lactose yields the ordinary reduction tests with Fehling's solution and other reagents, and the quantity present is seldom more than 1 to 2 per cent. With Fehling's solution the reduction is somewhat more tardy than that due to a corresponding percentage of glucose.

As with glycosuria, the polarimeter shows the urine to be dextro-rotatory.

Being a disaccharid, lactose does not undergo fermentation by yeast until it is split up into its constituents, glucose and galactose, and no fermentation occurs in the period of twenty-four hours usually allowed. It is preferable to employ pure cultures of yeast for this test, rather than the commercial kind, which may bring about some fermentation within the allotted time. With phenyl-hydrazine lactose forms an osazone, soluble in hot water, which melts at 200° C. and forms fine acicular crystals grouped into rosettes. However, von Jaksch (3) states that this osazone cannot be obtained from the urine in cases of lactosuria, in which the output of lactose is never large. If, however, as Ruizard (4) showed, the lactose be split up into its constituent sugars by means of hydrochloric acid, their osazones of these may be obtained. When the liquid is filtered whilst still hot, the glucosazone remains upon the filter, whereas galactosazone, which melts at 188–191° C. and has a characteristic crystalline form, only separates after the filtrate has cooled.

The presence in urine of a sugar which is dextro-rotatory, does not ferment with yeast within twenty-four hours, and does not yield a crystalline osazone with phenyl-hydrazine, will suggest that the case is one of lactosuria, provided always that the conditions are present with which this variety of mellituria is associated. Further confirmation may be obtained by means of Rubner's test, which is performed as follows: Some solid neutral lead acetate is added to the urine, which is afterwards boiled for some time. Ammonia is then added to the boiling liquid. If lactose be present a rose-red colour appears; glucose gives a coffee-brown colour, and maltose a pale yellow; with laevulose no colour-reaction is obtained.

The lactosuria of nursing women is common enough, and indeed appears to occur in almost every case at some period of the puerperium. Thus F. J. McCann (5), who examined the urine of 100 nursing women, found some sugar in every case, most often on the fourth day after delivery.

The most conspicuous lactosuria is met with when lactation is suddenly arrested, as when a nursing mother is admitted to a hospital. The phenomenon is clearly due to the absorption of constituents of the milk from the mammary glands, and it is a well-recognized fact that lactose, as a disaccharid, is scarcely at all burnt in the organism, unless it has been inverted in the alimentary canal and thence absorbed as its constituent sugars, glucose and galactose. Such lactosuria has no pathological significance, and owes its sole clinical importance to the possibility of its being mistaken for glycosuria; or of a true glycosuria being lightly dismissed as a physiological excretion of milk-sugar.

The occurrence of lactosuria during pregnancy is less well established. Obviously, it is only to be expected at the very end of the period, when the mammary glands are awakening to activity. Ney (6), who made some 150 examinations of parturient women, states that, in exceptional cases, sugar appeared in the urine even before delivery, and that the cases in which this occurred were in women with well-developed breasts, from which milk could already be expressed at the time. Lamaire (7), who employed the benzoylation method, which is capable of revealing the presence of very small quantities of sugars, failed to find lactose in any case in which he examined the urine before delivery, but this does not exclude its presence in exceptional cases, and the circumstances under which Ney found it strongly suggest that it is occasionally present at that period. Nevertheless, Ney did not determine the actual nature of the sugar excreted by his patients, and I am not aware that the fact that the sugar is actually lactose has been proved in any ante-partum case. The increasing attention which has been directed, of recent years, to true glycosuria occurring during pregnancy emphasizes the necessity of such demonstration.

Far less well recognized than the lactosuria of nursing women, is that met with in infants, which has an entirely different origin and is not devoid of pathological significance. Julius Grósz (8), who made a careful investigation of this phenomenon, and whose results were published in 1895, found an

abnormal reducing power of the urine in a considerable number of sucklings and showed that this was due to the presence of a carbohydrate. In healthy, breast-fed children it was not observed, whereas in those who suffered from digestive troubles, and especially from gastro-enteritis, the urine often had a strong reducing power, and yielded the sugar tests in a conspicuous manner, was optically active, but did not yield the fermentation test. He concluded that the sugar present was lactose, or a derivative thereof.

He further showed that the assimilation limit of normal sucklings for lactose is high, about 3·3 grammes per kilo of body weight during the first four weeks of life, whereas when digestive disturbances are present the limit is apt to be conspicuously lowered.

He ascribes this variety of lactosuria, which is clearly alimentary in its origin, in part to lowering of the assimilation limit, and in part to the influence of the bacteria of the alimentary canal upon the splitting of lactose therein, that portion which escapes inversion being absorbed and excreted as such.

Grósz did not adduce any evidence, other than that referred to above, that the sugar which the infants excrete is lactose, but Langstein and Steinitz (9) have since supplied the necessary proof that this is the case. They found that in almost every instance the excreted sugar was milk-sugar, and in three only of a series of fourteen cases was a second sugar present which, like lactose, was not fermented by yeast, and which yielded an osazone with phenyl-hydrazine which crystallized in delicate needles. This sugar they identified as galactose, and in one single case it constituted the bulk of the urinary sugar, glucose being only present in traces.

The ferment lactase, which effects the splitting of lactose into glucose and galactose, was found by Orban to be readily detectable in the stools of normal infants, whereas he failed to find it in those of children with gastro-intestinal disorders; an observation which suggested that absence of this ferment might be responsible for the excretion of lactose by infants suffering from such disorders. However, Langstein and Steinitz were unable to trace any relationship between this variety of lactosuria and the absence of lactose from the stools. The excretion of galactose, which was observed in some of their cases, they attribute to the fact that the assimilation limit for galactose is considerably lower than that for glucose, and in consequence it may well be supposed that, when the milk-sugar is inverted in the intestine, the galactose fraction is sometimes excreted in part as such, whereas the glucose is disposed of in the organism.

The alimentary lactosuria of infants is less likely to be met with in bottle-fed infants than in those nursed at the breast, owing to the smaller proportion of lactose usually present in the food of the former.

### *Maltosuria.*

Maltose, the disaccharid formed from two molecules of glucose with the loss of a molecule of water, may be regarded as an intermediate product between

starch and glucose, and it is in no way surprising that it should sometimes be excreted in the urine. Its detection in small quantities, in the presence of glucose, is by no means an easy matter, and it is not improbable that this sugar is a fairly common constituent of diabetic urines.

Maltose has a stronger dextro-rotatory power than glucose, but its reducing power is considerably less, and discrepancy between the results obtained by the two methods is one of the indications of its presence. When boiled with dilute acids the disaccharid is hydrolysed and changed to glucose, with the result that the urine which contains it becomes less optically active but gains in reducing power under such treatment. This affords a valuable means of detection and estimation, but it is necessary to ascertain that dextro-rotation and reducing power alike are removed by fermentation with yeast, and are due to a member of the sugar family.

Further evidence may be obtained by the preparation of the osazone soluble in hot water, by determining its melting-point, and by estimating its nitrogen content.

The occurrence of maltose in small amounts in diabetic urines has been described by Lépine and Boulud (10). Le Nobel (11) strongly suspected its presence in a urine in association with fatty stools, and in a few cases maltosuria has apparently been a symptom of definite pancreatic disease. A man, aged 49, who died of pyloric carcinoma and had two carcinomatous lymphatic glands in his pancreas, apparently excreted maltose and no glucose. von Ackeren (12), who investigated the case, obtained no osazone insoluble in hot water from the urine, but on cooling a crystalline product was obtained which melted at 193°–194° C. when slowly heated, at 206° when heated quickly, and darkened at 160° C. In these respects it resembled maltosazone. Rosenheim (13) has recorded a case of chronic interstitial pancreatitis with fatty stools in a man, aged 65, whose urine was examined by Flatow. A sugar was present, to the amount of 0·1 to 0·5 per cent. according to the diet given, which from the nitrogen content of its osazone was judged to be maltose.

C. Neuberg (14) refers to an unpublished case of Magnus Levy's in which the optical activity and reducing power of the urine did not agree with the figures required by glucose. By hydrolysis the dextro-rotation was diminished, but the reducing power was increased and came into accord with the requirements for a solution of glucose. Both the activity and reducing power of the urine were abolished by fermentation with yeast. The nature of the patient's disease is not mentioned.

The presence, in normal urine, of traces of isomaltose, a disaccharid which was obtained synthetically by Emil Fischer by condensation of glucose, has been rendered probable by the researches of several observers, including Pavy and Siau (15), but this sugar can as yet lay no claim to pathological importance.

*Laevulosuria.*

Of far more clinical interest than the forms of mellituria hitherto considered, are the conditions in which laevulose is excreted, with or without glucose.

For the detection of laevulose in urine the polarimeter is naturally of the greatest value. When no other sugar is present, the deflexion of the polarized ray to the left will correspond to the output of laevulose indicated by the reduction methods, but when both laevulose and glucose are present in association there may be only slight laevo-rotation, or the balance of the optical effects of the two sugars may render the urine inactive, or again, the more or less dextro-rotatory power may be retained, although less than would be the case if the reducing substance were all glucose.

Optical inactivity, under such circumstances, does not indicate the presence of equal quantities of glucose and laevulose, for the laevo-rotatory power of the latter is nearly twice as great as the dextro-rotatory power of the former.

The demonstration of the presence in urine of a laevo-rotatory substance which wholly or in part neutralizes the optical effect of the glucose does not necessarily imply that this substance is laevulose, for all known compound glycuronates are laevo-rotatory, although glycuronic acid itself deflects the polarized ray to the right; and $\beta$-oxybutyric acid, which is sometimes so abundantly present in the urine of diabetes, also has a strong laevo-rotatory power. However, neither of these substances undergoes fermentation by yeast, and if such fermentation abolishes, at the same time, the reducing power of the urine and its optical activity, we may be sure that the laevo-rotation is due to a sugar, presumably to laevulose. If, on the other hand, the impaired dextro-rotation of the urine be due to compound glycuronates, or to $\beta$-oxybutyric acid, laevo-rotation will persist after fermentation.

The well-known reaction of Seliwanoff has been much relied upon for the detection of laevulose. As originally described, this test is performed as follows: The urine is heated, for a short time, with an equal volume of strong hydrochloric acid and a few particles of resorcin, and the development of a red colour indicates the presence of laevulose. Various modifications of the test have been proposed by Rosin, Borchard, and others, and the following is that which Borchard (16) recommends:—

'A few cubic centimetres of urine are mixed with an equal volume of hydrochloric acid in a test tube, and boiled after the addition of a few particles of resorcin. If a red colour develops, the test tube is cooled in a stream of water, and its contents are poured into a dish or beaker and rendered alkaline by the addition of solid soda. The liquid is then returned to the test-tube and shaken with acetic ether. If laevulose be present the acetic ether acquires a yellow colour.'

The test, when so performed, is only conclusive in the absence of considerable quantities of indican and of nitrite. Neither of these substances alone yields the test, but when both are present a similar reaction is obtained to that yielded by laevulose.

Considerable doubt has been thrown upon the reliability of Seliwanoff's

test or its modifications when applied to urine. It may even be that, when glucose is present, a small quantity of laevulose may be actually formed therefrom by the boiling of the urine with hydrochloric acid, and that, from this cause, a positive reaction may be obtained, even when laevulose was not originally present (17).

Neuberg has shown that laevulose, being a ketonic sugar, yields a crystalline osazone with methyl-phenyl-hydrazine, whereas the aldoses do not do so. The obtaining of this osazone, which melts at 153° C., therefore affords the most conclusive evidence to be obtained of the presence of laevulose in the urine, short of its actual isolation in crystalline form, which has only once been accomplished. The ordinary phenyl-hydrazine test does not serve to differentiate laevulose from glucose, for both sugars yield the same osazone.

To sum up, in order that the presence of laevulose in the urine may be satisfactorily demonstrated it is necessary to show that a laevo-rotatory substance is present which yields the reduction tests of sugars, is fermented by yeast, gives Seliwanoff's reaction, and yields with phenyl-hydrazine the ordinary glucosazone, and with methyl-phenyl-hydrazine an osazone which melts after purification, at 153° C.

As has already been mentioned, the cases in which laevulose is excreted fall into several distinct groups.

When large doses of this, as of any sugar, are taken by the mouth—doses large enough to overstep the assimilation limit of the individual who swallows it—some will reappear unchanged in the urine. As is the case with glucose, the assimilation limit for laevulose may be conspicuously lowered by disease, but the morbid states which favour the occurrence of alimentary laevulosuria are not the same as those which lower the limit for glucose; and the researches of H. Strauss and others have revealed a conspicuous influence of hepatic derangements upon laevulose tolerance. Indeed it appears to be proven that the production of laevulosuria by comparatively small doses of this sugar serves as a definite indication that the liver is the seat of disease.

In many cases of diabetes, on the other hand, laevulose may, as is well known, be utilized to a considerable extent, although the power of dealing with glucose be very seriously diminished; and the administration of laevulose may even lead to storage of glycogen in the liver.

The researches of Rosin (18), Schlesinger (19), and others indicate that the excretion of small quantities of laevulose in association with far larger amounts of glucose is no uncommon event in diabetes mellitus. von Noorden (20) has seldom found evidence of its presence in the milder cases, but often in those of the severe kind. However, the results obtained by different investigators are not in full accord upon this point, and as the reaction of Seliwanoff has been almost exclusively relied upon for the detection of laevulose in such cases, anything which throws doubt upon the reliability of this reaction when applied to urine tends to diminish the value of the evidence of the frequent excretion of laevulose in diabetes.

The phenomenon of laevulosuria was first mentioned by Gorup Besanez in 1872, and in 1876 Zimmer (21) and Czapek (22) described cases in which the urine contained laevulose as well as glucose. In 1884 J. Seegen (23) recorded the case of a woman of nervous temperament whose urine yielded the sugar tests at times, and exhibited a laevo-rotatory power which was removed by fermentation with yeast. The quantity of sugar, estimated as glucose by Fehling's method, was 1·08 per cent. Kulz (24), who made a further examination of the urine of the same patient in 1891, came to the conclusion that the reducing substance was, in all probability, laevulose.

The more recent cases, some of which have been far more thoroughly investigated than the earlier ones, and in some of which the presence of laevulose in the urine has been established beyond all question, have differed among themselves in certain noteworthy respects. They fall into two main groups, which are distinguished by the effects of the administration of laevulose by the mouth. Some have been cases of mixed mellituria, to employ Otto Neubauer's term, in which, in addition to noteworthy quantities of laevulose, glucose has been present in the urine; whereas in other cases laevulose has appeared to be the only sugar excreted.

The limits of these groups are not very easily defined, for we are confronted, on the one hand, with cases of glycosuria with mere traces of glucose in the urine, and, on the other hand, with cases of apparently pure laevulosuria which, from their behaviour towards ingested sugars, would seem to belong rather to the mixed mellituria class.

In all the recorded cases, carbohydrate-free diet has brought about a disappearance of sugar from the urine, and in some the mixed mellituria appears to have been a transitory phenomenon.

The quantity of sugar excreted has as a rule been small, some 1 or 2 per cent., and the daily output of urine has not been excessive, but in some cases symptoms usually associated with diabetes have been present, and in others nervous disturbances of more or less obvious kinds.

In the cases of one class, mostly obvious examples of mixed mellituria, the administration of laevulose by the mouth, in doses such as are wont to overtax the tolerance even of normal individuals, caused no increase of the laevulose excretion. From this it is evident that in such cases we are dealing with no mere alimentary laevulosuria, due to a lowering of the assimilation limit for laevulose.

Thus, in a case which Otto Neubauer (25) describes, doses of 50 grammes of laevulose were disposed of practically completely, and in Rosin's case even as large a dose as 100 grammes caused no increase of the output. May obtained a similar result with his patient; Lion (26) found only a slight increase of laevulose in the urine when that sugar was taken by the mouth, and von Moraczewski (27) has recently described a similar result in a case which he regarded as one of pure laevulosuria, basing this opinion upon the relation of the optical activity of the urine to its reducing power.

In a case under the observation of the writer, in which small quantities of glucose and laevulose are excreted together, and in which the urine is on some days optically inactive, and on others has a slight dextro- or laevo-rotatory power, the laevo-rotation and reducing power were alike unaffected by the administration of 50 grammes of laevulose by the mouth.

The effects of the administration of glucose to such patients have been less uniform. In the cases recorded by Rosin (28) and May (29) respectively, glucose taken by the mouth, even up to 100 grammes, caused no increased output of sugar, and in von Moraczewski's case the increase due to glucose, like that due to laevulose, was very small. Otto Neubauer, on the other hand, observed a conspicuous increase of the output of both glucose and laevulose when his patient with mixed mellituria took glucose by the mouth, whereas laevulose caused no such increase; from which it would appear that glucose was in part converted into laevulose in the organism and was excreted as such, a conversion which presents no special difficulty on chemical grounds. In the same case an injection of phloridzin brought about an excretion of both sugars in the urine, whereas in ordinary individuals the sugar excreted after such injections is glucose alone.

The patient was found to have an assimilation limit for glucose, although a low one, some 15 to 25 grammes being required to bring about reappearance of sugar when the urine was rendered sugar free by dieting, and on the other hand, as we have seen, the assimilation limit for laevulose was not below the normal. Thus the difference between this case and those of Rosin and May was rather one of degree than of kind.

It is not easy to understand why, in cases in which neither glucose nor laevulose increase the urinary sugar, a carbohydrate-free diet should abolish the mellituria.

Of the clinical course of the condition under discussion we as yet know scarcely anything, save that it appears to run a mild course, to be amenable to dietetic treatment, and not to be attended by any of the graver symptoms of the diabetic state. All that we do know suggests that we are here dealing with a malady or anomaly wholly distinct from the ordinary forms of diabetes, and the subject offers a promising field for further investigations.

Three most interesting examples of pure laevulosuria have been investigated by Otto Neubauer (30), Schlesinger (31), and Lépine and Boulud (32) respectively. The effect of the administration of sugars to these patients shows clearly that the cases belong to a class wholly distinct from those which we have hitherto been considering.

Neubauer's patient was a man, aged 30, who exhibited symptoms suggestive of diabetes, including loss of flesh and nervous disturbances. Schlesinger's patient was a girl of 15 who came under treatment on account of a spinal curvature, and that of Lépine and Boulud a woman, aged 32, in whom the laevulosuria apparently followed a still-birth. In all three cases the presence of laevulose in the urine was fully proven, and there was strong evidence that laevulose was the only sugar excreted.

In all three the urine was strongly laevo-rotatory, yielded Seliwanoff's reaction in a pronounced manner, and reduced Fehling's solution. Moreover, the optical activity, power of yielding Seliwanoff's reaction, and reducing property were all removed by fermentation with yeast. The estimations by reduction and by polarimetry were in full accord on the assumption that the reducing substance consisted wholly of laevulose.

With phenyl-hydrazine, in each case, an osazone was obtained which had the melting-point of glucosazone; and Lépine and Boulud and Otto Neubauer obtained with methyl-phenyl-hydrazine the characteristic osazone of laevulose, which melts at 153° C.

Lépine also obtained the crystalline calcium compound of the sugar, and Neubauer succeeded in isolating the laevulose in crystalline form, which had never previously been done in any case of laevulosuria.

The crystals obtained were soluble in absolute alcohol, and further proof of their nature was furnished by the fact that they were insoluble in a saturated alcoholic solution of laevulose, and by their crystalline form, refractive power, and specific gravity.

In all three cases a carbohydrate-free diet brought about disappearance of the sugar from the urine, and in all the mere withdrawal from the diet of laevulose, of articles of food which contain it, and of cane sugar of which it is a constituent, sufficed to produce the same effect.

In the cases of Schlesinger and Neubauer (in Lépine's case such tests were not applied) a diet rich in starch and the administration of large doses of glucose failed equally to increase the output of sugar in the urine; whereas both laevulose and saccharose when given by the mouth caused a pronounced increase. It is further remarkable that inulin, a polysaccharid which stands to laevulose in a similar relation to that of starch to glucose, caused no increase of the laevulosuria in either case.

Schlesinger made the most interesting observation that his patient responded to an injection of phloridzin by excreting glucose, as does a normal man, whereas the laevulose excretion showed no increase; and he justly points out that this result can hardly be reconciled with the widely held view that phloridzin glycosuria is merely due to escape by the kidneys of the normal sugar content of the blood. It will be remembered that in Neubauer's case of mixed mellituria phloridzin increased the output of both sugars, and this supplies a further point of difference between the two groups. In his case of pure laevulosuria no injection of phloridzin was given.

Here, then, we are confronted with a form of alimentary laevulosuria, and not with a conversion of glucose into laevulose in the organism.

It is one of the most remarkable features of Neubauer's case of pure laevulosuria, in which alone the point was investigated, that, although the patient retained a considerable power of dealing with ingested laevulose, his assimilation limit for that sugar was zero. When, as a result of dieting, the urine was sugar free, any dose of laevulose, however small, produced laevulosuria,

and whatever the dose given the fraction thereof excreted was practically constant. Some 15–17 per cent. of any quantity taken, from 3·8 up to 50 grammes, appeared unchanged in the urine. In Schlesinger's case 12·5 per cent. of a dose of 90 grammes of laevulose appeared in the urine.

Neubauer's observations suggest that some definite fraction of the laevulose taken escaped destruction in the ordinary manner, and whilst speaking with all reserve as to the causation of this phenomenon, he points out that it would appear that laevulose, when given by the mouth to a normal individual, is in large part stored as glycogen and ultimately changed to glucose, whereas part is directly burnt: and it is noteworthy that the researches of Johannson, Billström, and Heyl indicate that when a large dose of laevulose or of dextrose is taken by a normal man an increased excretion of carbon dioxide results, which corresponds to about 15 per cent. of the sugar taken. This fraction, which corresponds so strikingly with the fraction excreted by the laevulosuric patient, must be supposed to represent the portion of the ingested sugar which is directly burnt. Neubauer was unfortunately not able to put the hypothesis to a crucial test by determining the $CO_2$ output of his patient, which should, if the suggested explanation were the correct one, have been unaffected by the administration of laevulose.

It cannot be assumed that all cases of pure laevulosuria fall into this latter group, and all cases of mixed mellituria into the former one, for, more recently, von Moraczewski (33) has observed a case in which, judging by the relation of reducing power to optical activity of the urine, laevulose was alone excreted, but which agreed with some of the recorded examples of mixed mellituria, in that neither glucose nor laevulose, given by the mouth, caused more than a trifling increase of the sugar excretion.

In conclusion it should be mentioned that on a diet free from laevulose and saccharose Neubauer's patient not only ceased to excrete laevulose, but improved in general health, gained flesh, and felt well.

### *Pentosuria.*

A very special interest attaches to the rare cases in which a sugar is found in the urine which is neither a mono- nor a disaccharid of the hexose group, such as those which we have hitherto been considering, but is built up upon a chain composed of an uneven number of carbon atoms. The pentoses, or five-carbon sugars, play important parts in vegetable metabolism and are met with in many vegetable structures in the form of complex anhydrides, or polysaccharids, known as pentosanes. Two members of this group, racemic arabinose and *l*-xylose, are now recognized as products of animal metabolism also.

*l*-Xylose was found by Hammarsten in the pancreas, and its exact nature was determined by C. Neuberg. It is probable that the pentose sugar present in many other organs and structures is of this same nature, but it is not yet known with certainty whether this is the case. In the metabolic anomaly known as pentosuria, on the other hand, the sugar excreted is arabinose, and,

except in cases which are merely alimentary, is almost invariably the optically inactive, racemic, variety of that sugar.

The first case of pentosuria recognized as such was described by Salkowski and Jastrowitz (34) in the year 1891; and some thirty examples are now on record, not one of which has been observed in this country. In the great majority of instances the patients have been regarded as sufferers from a mild form of diabetes and treated accordingly.

It is necessary to draw a sharp distinction between the essential pentosuria here referred to, which is in no way dependent upon the ingestion of pentoses or pentosanes, and the alimentary cases due to a mere overtaxing of the power of the organism to deal with such sugars; which power is much less than that of destroying the monosaccharids of the hexose group.

Even so small a dose as one gramme of arabinose is followed by the appearance of a small quantity of the sugar in the urine; and the free consumption of certain fruits, such as cherries or plums, or the drinking of a litre or more of an unfermented fruit juice, suffices to set up an alimentary pentosuria. In such circumstances the sugar excreted is dextro-rotatory, as is the arabinose present in the fruits consumed. It must be remembered that, as was pointed out in the beginning of this article, this dextro-rotatory pentose is styled *l*-arabinose, on account of its chemical relationships, although the name is at variance with its own optical property.

Kulz and Vogel (35) were able to obtain from large volumes of some diabetic urines small yields of an osazone, soluble in hot water, which from its melting-point and nitrogen content appeared to be a pentosazone, and also found the same substance in the urine of dogs from which the pancreas had been removed. No information as to the exact form of pentose here excreted is as yet forthcoming, and some other observers have failed to find such a sugar in the urine of diabetics (36).

Cammidge (37) believes that the substance which he has found to be present in the urine of patients with pancreatitis, and which yields a crystalline osazone after the urine has been boiled with hydrochloric acid, is a pentose. He extracted this substance from large specimens of urine, and found that it gave the ordinary sugar reactions and was optically inactive. The nitrogen content of the osazone agreed with that of a pentosazone, but the melting-point of this compound was 178–180° C., whereas that of the pentosazones is between 156° and 160°. The phloroglucin test gave a red colour and the absorption band, but with the orcin test and Bial's modification thereof no green colour was obtained, although a spectroscopic band between C and D was observed.

In cases of true pentosuria the urine reduces Fehling's solution, usually like one containing some 0·5 per cent. of glucose. The reaction is apt to be delayed, and often occurs suddenly after boiling for a time, or whilst the mixture of urine and reagent is cooling. This has been regarded as a characteristic of such urines, but Bial (38), who had an exceptionally large experience in this matter, stated that this manner of reduction was best marked in specimens which had

been kept for some time with preservative agents, such as toluene, whereas in fresh specimens of urine reduction sometimes occurs even before the boiling-point is reached.

Pentose urines also yield Nylander's and the saffranin tests.

With yeast no fermentation occurs, and the urine is optically inactive. In only one of the cases of essential pentosuria hitherto investigated, that recorded by Luzzato (39), was the sugar present dextro-rotatory, presumably *l*-arabinose. With phenyl-hydrazine an osazone is obtained, soluble in hot water, and which, after recrystallization, melts at about 160° C.

Certain special colour-reactions are of much value in the detection of pentoses. Thus, when half a cubic centimetre of the urine is added to 5 or 6 c.c. of fuming hydrochloric acid containing a small quantity of phloroglucin, and the containing test-tube is placed in a beaker of boiling water, a deep red colour appears if a pentose be present, and a spectroscopic absorption band is seen, lying between the Fraunhofer lines D and E.

The orcin test gives more satisfactory indications, and of this test Bial's modification, which is specially well suited for clinical purposes, is carried out as follows: Bial's reagent is prepared by dissolving 1 gramme of orcin in 500 c.c. of hydrochloric acid of sp. gr. 1·151, and adding 25 drops of a 10 per cent. solution of ferric chloride. It is necessary that the ingredients should be in accurate proportions, and that the hydrochloric acid used should be of the prescribed strength.

Some 5 c.c. of this reagent are heated to boiling in a test-tube, and after the tube has been removed from the flame five drops of the urine are added from a pipette. If a pentose be present a green ring quickly appears at the junction of the liquids, and if the tube be gently shaken spreads through the liquid, which then shows an absorption band between the C and D lines. With the above tests available the detection of pentose in urine would present little difficulty were it not that glycuronic acid yields similar colour-reactions. However, compound glycuronates are laevo-rotatory, do not yield an osazone with phenyl-hydrazine, and with them the colour-reactions are only obtained when the glycuronic acid is set free by boiling with the acid reagent. The phloroglucin test is much less distinctive than that with orcin, and it is claimed for Bial's test that, provided it is performed in the manner described, it is quite distinctive, although if boiling be continued after the urine has been added the green colour will be obtained with urines containing compound glycuronates. If there be any doubt upon this score, it may be removed by obtaining the osazone and determining the percentage of nitrogen which it contains, viz. 17·07 per cent. in the case of a pentosazone.

To clinical workers it is clearly a matter of considerable importance whether or no Bial's test may be confidently relied upon for the detection of pentose as distinguished from glycuronic acid. At present it is hardly safe to rely upon any single test for this purpose, and laboratory methods must still be invoked if certainty is to be obtained. On the other hand, it may safely be con-

cluded that a reducing substance in urine which does not yield Bial's reaction is not a pentose.

The unsatisfactory way in which the precipitate of cuprous hydrate separates renders Fehling's method unsatisfactory for the estimation of pentose in urine, and other methods such as those of Knapp and Allihn have to be resorted to. Moreover, C. Neuberg (40) has shown that no reduction method gives a true measure of the quantity of arabinose present, because it is in part excreted as a ureide, and this part only reduces after the ureide has been broken up by heating with an acid.

It is important that the occurrence of pentosuria should be recognized in practice, in spite of its great rarity, and it is also important that the cases should be identified as such; for although some of them have occurred in members of diabetic families, there is no doubt that the two conditions are wholly distinct, and the dietary restrictions, which are of so great value and importance in diabetic cases, are unnecessary and uncalled for in pentosuria. There are, indeed, no morbid symptoms which are directly attributable to pentosuria, unless neurasthenic manifestations should be classed as such, and the evidence available suggests that it should be regarded less as a disease than as a congenital anomaly, and classed with such conditions as alkaptonuria and cystinuria. It is true that no case of pentosuria has yet been recognized in a child, but it is wont to occur in several brothers and sisters of a family, and there is reason to believe that there is a special liability of the Jewish race.

It has been conclusively shown that the withdrawal of carbohydrates from the diet has no influence upon the excretion of pentose by pentosurics, and there is little to indicate that any other food-constituents increase the output. The administration of glucose and of other sugars, even in large doses, was found by Blumenthal and Bial (41), af Klerker (42), and others, to cause an increase of the reducing power of the urine, and Bial and Blumenthal further showed that when 5 grammes of *l*-arabinose were administered by the mouth, the amount of optically active pentose which appeared in the urine was no greater than when a like dose was taken by a normal individual.

Hence it would appear that a pentosuric has no less power of burning arabinose entering by the alimentary canal than has a normal subject, just as a cystinuric is able to destroy swallowed cystin. The parent substance of the racemic arabinose which pentosurics excrete is still unknown, and the fact that such individuals excrete an inactive sugar, which is itself sufficiently remarkable, is rendered more puzzling by the observations of Neuberg and Wohlgemuth (43), who found that when this same sugar, racemic arabinose, was administered to a normal man he excreted more of the laevo-rotatory constituent, racemic arabinose, than of the dextro-rotatory constituent, and the urine, which had previously been optically inactive, acquired a conspicuous laevo-rotatory power.

Neuberg (44) has advanced the hypothesis that the parent substance may be galactose. Arabinose bears a relationship to galactose similar to that of xylose to glucose, and for chemical reasons, which are too technical to be here discussed,

it is easier to suppose that racemic arabinose should be formed from galactose than from any other member of the carbohydrate group. Since the pentose is clearly not derived from the food, its origin must be sought for in some product of tissue metabolism formed within the organism, and that galactose is so formed is well known. However, there is not as yet any direct evidence in support of this hypothesis, nor has the administration of galactose, either as such or in lactose, been found to have any obvious effect upon the excretion of arabinose by pentosuria.

*Heptosuria.*

In a case which was recently described by Rosenberger (45) a sugar was excreted in the urine which differed in its properties from any of those which have hitherto been referred to in this article. The patient who excreted it was a woman, aged 50 years, who presented symptoms suggestive of pancreatic disease, and which raised a suspicion that a pancreatic calculus existed. She had recurrent attacks of colicky pains, and occasionally passed pale stools rich in fat and poor in bile derivatives. She also exhibited bronzing of the skin.

The urine, which was scanty in amount, reduced Fehling's solution freely at times. The polarimeter showed that the sugar present was optically inactive, and only when small quantities of glucose were also present, as was sometimes the case, was slight dextro-rotation observed. With pure yeast no fermentation occurred, save when glucose was present. The quantity of sugar varied widely on different days. Acetone and aceto-acetic acid were present in the urine.

The urine did not give Seliwanoff's laevulose reaction, nor the colour-reactions of a pentose, and from it an osazone was obtained which became brown at 190° and melted at 195° C. Analyses of this product yielded figures which agreed with those to be expected if the sugar contained therein were a heptose, or seven-carbon sugar. Emil Fischer has synthesized several heptoses of which the osazones melted at 195°, after becoming brown at 190°, and, like that obtained by Rosenberger, were sparingly soluble in boiling alcohol.

Rosenberger suggests that the sugar found in urine by Leo in association with glucose, to which he gave the name of laiose, which had similar properties save that it was optically active, was the laevo-rotatory variety of the same sugar which was, in the case under discussion, excreted in the racemic form.

He further pointed out that in his case the heptosuria was no harmless anomaly, such as pentosuria appears to be, but a symptom associated with grave illness, and in all probability with disease of the pancreas.

It remains to be seen whether future investigations will reveal further cases of the kind, and will confirm the view that the sugar excreted was a member of the heptose group. Such sugars have not hitherto been recognized as products of animal metabolism, but the same might have been said of the pentose sugars as recently as twenty years ago.

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